FDA Recognition that Hydrocortisone is Safe and Effective as an OTC Antipruritic Active Ingredient at Concentrations up to 1.0 Percent

55 FR 6932

February 27, 1990

In response to a citizen petition, FDA agreed that hydrocortisone can be considered safe an effective as an OTC antipruritic active ingredient at concentrations greater than 0.5 percent up to a maximum of 1.0 percent. FDA's reasoning and conclusions were published in volume 55 of the Federal Register. This publication dealt exclusively with the safety and effectiveness of hydrocortisone and is attached in its entirety.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 348

[Docket No. 78N-301H]

RIN 0905-AA06

External Analgesic Drug Products for Over-the-Counter Human Use; Amendment of Tentative Final Monograph

AGENCY: Food and Drug Administration, NNS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking amending the tentative final monograph (proposed rule) for over-the-counter (OTC) external analgesic drug products. This proposed rulemaking would establish conditions under which products containing hydrocortisone or its hydrocortisone acetate equivalent for topical use in concentrations from 0.25 to 1 percent are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering a citizen petition [Docket No. 78N-0301/CP00005] that requested OTC status for products containing hydrocortisone above 0.5 percent up to 1 percent. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by April 30, 1990. Written comments on the agency's economic impact determination by April 30, 1990.

ADDRESSES: Written comments, objections, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of December 4, 1979 (44 FR 69768), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC external analgesic drug products, together with the recommendations of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (the Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. Interested persons were invited to submit comments by March 6, 1980. Reply comments in response to comments filed in the initial comment period could be submitted by April 3, 1980.

In the advance notice of proposed rulemaking, the Panel recommended that hydrocortisone and hydrocortisone acetate be categorized as safe and effective for antipruritic use at concentrations of 0.25 to 0.5 percent. The Panel provided a chart of the controlled studies that demonstrated effectiveness of topical hydrocortisone (44 FR 69768 at 69822) and noted that a 1-percent concentration of hydrocortisone was used in a number of these studies.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC external analgesic drug products was published in the **Federal Register** of February 8, 1983 (48 FR 5852). In that tentative final monograph, the agency agreed with the Panel and tentatively concluded that hydrocortisone and hydrocortisone acetate at concentrations of 0.25 to 0.5 percent were safe and effective for the proposed OTC uses and that the benefits of OTC availability outweigh any potential misuse that may occur (48 FR 5854).

Subsequently, the agency received a citizen petition (Ref. 1) containing additional safety and effectiveness data in support of OTC status for 1 percent hydrocortisone and hydrocortisone acetate equivalent to 1 percent hydrocortisone. FDA has evaluated these data and, in this amendment to the tentative final monograph, is stating its position on hydrocortisone 1 percent and hydrocortisone acetate equivalent to 1 percent hydrocortisone for OTC use. Final agency action on this matter will occur with the publication at a future data of a final monograph, which will be a final rule establishing a monograph for OTC external analgesic drug products.

Although the agency is proposing in this amendment to the tentative final monograph to switch hydrocortisone at a concentration above 0.5 percent up to 1 percent and hydrocortisone acetate equivalent to above 0.5 percent up to 1 percent hydrocortisone from their present status as prescription drugs, currently subject to an approved new drug application, to OTC status, OTC marketing may not begin at this time. In the **Federal Register** of June 3, 1983 (48 FR 24925), FDA explained the enforcement policy for drugs that were originally on prescription status but which were being proposed for OTC marketing under the OTC drug review. As noted there, 21 CFR 330.13 permits OTC marketing of a drug previously limited to prescription use prior to publication of a final monograph provided that certain conditions are met. To qualify for such treatment, the drug must, at a minimum, have been considered by an OTC drug advisory review panel and either been recommended for OTC marketing by the panel or subsequently determined by FDA to be suitable for OTC marketing. Hydrocortisone at a 1-percent concentration and above was evaluated by the Panel in its consideration of the prescription-to-OTC switch of hydrocortisone preparations; however, the Panel recommended that the concentration of OTC drug products be limited to 0.25 to 0.5 percent hydrocortisone (44 FR 69768 at 69813 to 69824).

Hydrocortisone 1 percent and hydrocortisone acetate equivalent to 1 percent hydrocortisone were also specifically considered by the Dermatologic Drugs Advisory Committee (the Committee) at its meeting held on November 18, 1985 (Ref. 2), but the Committee did not recommend OTC marketing status because of concerns about adverse reactions not being recognized or reported, inappropriate promotion, credibility of advertising, and appropriate labeling.

FDA concludes that public comments submitted in response to the proposed switch in status should be evaluated before a final agency decision on OTC status is made and before OTC marketing begins. Therefore, hydrocortisone above 0.5 percent up to 1 percent and hydrocortisone acetate equivalent to above 0.5 percent up to 1 percent hydrocortisone do not qualify for early OTC marketing under the terms of the enforcement policy set out in § 330.13. Until the comments to this proposal are reviewed, hydrocortisone above 0.5 percent up to 1 percent and hydrocortisone acetate equivalent to above 0.5 percent up to 1 percent hydrocortisone remain prescription drugs subject to the terms and conditions specified in their approved applications.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the

Federal Register. On or after that date, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

If the agency determines that any labeling for a condition included in the final monograph should be implemented sooner than the 12-month effective date, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular condition, a shorter deadline may be set for removal of that condition from OTC drug products.

I. Background Information

A. Introduction

Hydrocortisone has been marketed in the United States since 1952 as a prescription drug. On December 4, 1979, FDA's Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products recommended to the agency that hydrocortisone could be considered safe and effective for OTC use at concentrations of 0.25 to 0.5 percent (44 FR 69768). Based on the Panel's recommendations, the agency allowed OTC marketing of products containing 0.25 to 0.5 percent hydrocortisone to begin on December 4, 1979. During the years of OTC marketing, it has been shown from the experience of consumers and physicians, and from data from clinical investigators, that 0.25- to 0.5-percent concentration of hydrocortisone does not provide the optimal therapy in all individuals for all the conditions for which the drug may be used. It has been suggested that a 1-percent concentration of hydrocortisone would provide a more effective treatment for pruritus and inflammation associated with the conditions listed in the current labeling for the lower concentrations of hydrocortisone and hydrocortisone acetate (i.e., the temporary relief of itching associated with minor skin irritations and rashes due to "eczema," "insect bites," "poison ivy, poison oak, or poison sumac," "soaps," "detergents," "cosmetics," "jewelry," and external "genital," "feminine," and "anal itching"). As a result, FDA has received several requests to amend the tentative final monograph for OTC external analgesic drug products to include 1 percent hydrocortisone and hydrocortisone acetate for OTC use.

B. Petition To Amend Tentative Final Monograph

The citizen petition requesting OTC marketing status for hydrocortisone 1 percent and hydrocortisone acetate equivalent to 1 percent hydrocortisone, as antipruritic active ingredients in cream, ointment, lotion, and spray dosage forms, was submitted on May 26, 1987 (Ref. 3). The petitioner pointed out that, after 7 years of OTC marketing, 0.5 percent hydrocortisone may not provide optimal therapy for the various conditions for which it is indicated, that 1 percent hydrocortisone would be more effective (based on consumer experience and data in the literature), and that risks are estimated to be minimal while benefits would be substantial. The petition discussed the history of hydrocortisone use, its safety and effectiveness, its approval for OTC use in foreign countries, drug experience reports, and the proposed OTC labeling. The petition included extensive data and information from published studies on issues related to the safety and effectiveness of topical hydrocortisone.

In further support of the petition to switch 1 percent hydrocortisone from prescription to OTC status, a manufacturers' association provided additional information (Ref. 4) which it believed would be helpful to the agency in evaluating the citizen petition. The association stated that the additional data provide further support that optimal therapy can be provided by the 1-percent concentration of hydrocortisone and that consumers will not be at any additional risk by the marketing of a more effective product for pruritic conditions indicated on current OTC drug product labels for 0.5 percent hydrocortisone. The manufacturers' association noted that over 130 million OTC units of 0.5 percent hydrocortisone had been bought in this country to date, and most of the negative reports received by manufacturers of these products involved a lack of effectiveness.

After carefully reviewing the safety and effectiveness data and other information submitted, the agency tentatively concludes that they support a proposal to amend the tentative final monograph for OTC external analgesic drug products in 21 CFR part 348 to include concentrations above 0.5 up to 1 percent hydrocortisone and hydrocortisone acetate equivalent to 0.5 to 1 percent hydrocortisone. Accordingly, the agency is publishing this notice of proposed rulemaking to invite public comment on the proposed switch of concentrations of hydrocortisone above 0.5 percent up to 1 percent from prescription to OTC status.

C. The Panel and Committee Deliberations

The Panel's report indicates that the first effort to change hydrocortisone to OTC status occurred in 1956 (44 FR 69768 at 69813). Public hearings were held from August 15 to 17, 1956, to examine a petition request for possible transfer to OTC status. Based on these hearings, the petition was denied in the **Federal Register** of January 17, 1957 (22 FR 353).

At its January 21, 1975 meeting, the Panel was informed that no one among the physicians contacted had any strong feelings against hydrocortisone being OTC (Ref. 5). At the May 22, 1975 meeting, there was an extended discussion whether the Panel ought to recommend a higher concentration than 0.5 percent (Ref. 6). However, at the March 4 through 5, 1976 meeting, the Panel voted not to approve 1 percent hydrocortisone for OTC status by a vote of 5 to 1 with 1 abstention and approved 0.25 to 0.5 percent hydrocortisone for OTC status by a vote of 6 to 1 (Ref. 7). The Panel's decision at that time was based on the fact that there was no marketing history for hydrocortisone at any concentration for OTC use. At its final meeting on May 22 and 23, 1978, the Panel adopted its report on external analgesic drug products for OTC use, which included its recommendation for 0.25 to 0.5 percent hydrocortisone for OTC status (Ref. 8).

Two other OTC drug advisory review panels proposed 1 percent hydrocortisone for inclusion in OTC drug monographs. The Advisory Review Panel on OTC Miscellaneous External Drug Products (Miscellaneous External Panel) proposed 0.25 to 1 percent hydrocortisone for use (e.g., to relieve itching) on dandruff, seborrheic dermatitis, and psoriasis, but classified the ingredient in Category III because the studies were inadequate to support effectiveness for this use (47 FR 54646 at 54674 and 54675). The Advisory Review Panel on OTC Antimicrobial II Drug Products (Antimicrobial II Panel) recommended combinations of up to three antifungals with hydrocortisone

0.5 to 1 percent for fungal infections of the skin (47 FR 12480 at 12554 and 12555). However, the agency dissented from the Antimicrobial II Panel's recommendation (47 FR 12481).

At the November 18, 1985 meeting of the Dermatologic Drugs Advisory Committee (the Committee) (Ref. 9), the question of whether to switch 1 percent hydrocortisone from prescription to OTC status was discussed. Four physicians spoke in favor of the switch. The reasons given were that most people make rational decisions about home treatment; there had been no toxicity from local absorption, no abuse, no serious local or systemic side effects, and no exacerbation of local infection with 1 percent; that local toxicity resulted only when the drug had been applied for 3 or 4 months; and 0.5 percent products had not been effective for some uses. However, one physician stated the following caveats: the product should not be labeled for use around the eyes or for use on infants and small children. The Committee felt that greater absorption results from these uses with a potential for ocular, cutaneous, and systemic toxicity.

Two physicians (one presenting the position of the American Academy of Dermatology) spoke in opposition to the OTC status of the 1-percent concentration (Ref. 2). They expressed several concerns: (1) consumers would find the 1-percent product more effective than the 0.5 percent and thus tend to use the product for prolonged periods, which would lead to greater absorption and adverse effects, (2) potential use in some products of vehicles that enhance absorption of hydrocortisone, and (3) inappropriate advertising.

On the question of switching 1 percent hydrocortisone from prescription to OTC status, the Committee vote resulted in a tie (4 to 4). Most members felt that the drug was safe and effective. However, there were concerns about adverse reactions not being recognized or reported, inappropriate promotion, advertising credibility, and appropriate labeling (Ref. 9). One committee member pointed out that side effects were not reported because they were minimal and not significant and, therefore, were ignored. Another member would have voted for 1 percent hydrocortisone becoming OTC if there could be assurance about the advertising and labeling issues. Still another member referred to the Panel's opinion that OTC drug products should contain the lowest effective dosages, and pointed out that 0.5 percent hydrocortisone was not effective in most cases in 15 years of practice, implying that 1 percent hydrocortisone was the lowest effective dose.

The Federal Trade Commission (FTC), not FDA, is the agency that has the primary responsibility for regulating OTC drug advertising. However, FDA has the authority to regulate OTC drug advertising that constitutes labeling under the Federal Food, Drug, and Cosmetic Act (the act). See, e.g., *United States* v. *Article of Drug . . . B-Complex Cholinos Capsules*, 362 F.2d 923 (3d Cir. 1966); *V.E. Irons, Inc.* v. *United States*, 244 F.2d 34 (10 Cir.); *cert. denied*, 354 U.S. 923 (1957). In addition, for an OTC drug to be generally recognized as safe and effective and not misbranded, the advertising for the drug must satisfy the FDA regulations in § 330.1(d) (21 CFR 330.1(d)), which state that "The advertising for the product prescribes, recommends, or suggests its use only under the conditions stated in the labeling."

Although the Panel had discussed advertising and promotion of OTC hydrocortisone, its report did not include any statements of concern about either advertising or promotion of such products. The agency has considered the advertising of hydrocortisone-containing drug products over the ten years since these products were first marketed OTC and has not observed any major problems regarding advertising or promotion. The agency has contacted FTC (Ref. 10) and that agency also has not observed any major problems regarding advertising or promotion of OTC hydrocortisone drug products. Based on the above, the agency does not consider hypothetical advertising problems to be sufficient basis to disallow the OTC marketing of drug products containing above 0.5 percent up to 1 percent hydrocortisone.

D. Tentative Final Monograph for OTC External Analgesic Drug Products

The agency included hydrocortisone and hydrocortisone acetate at concentrations equivalent to 0.25 to 0.5 percent hydrocortisone in the tentative final monograph for OTC external analgesic drug products that was published in the **Federal Register** of February 8, 1983 (48 FR 5852). During the comment period following publication of that proposal, the agency did not receive any comments relating to the switch of 1 percent hydrocortisone to OTC status.

E. Foreign Marketing Experience

The petitioner and the manufacturers' association have indicated that 1 percent hydrocortisone for OTC use has been approved in several foreign countries: Sweden (1983), Denmark (1984), Norway (1985), and Great Britain (1986). In addition, a "switch petition" is currently under review in Germany. Information regarding the basis for approval for OTC marketing in Sweden and Great Britain was provided (Ref. 11).

Hydrocortisone at a maximum strength of 1 percent was switched from prescription-to-OTC marketing status in Sweden on October 1, 1983. However, information was provided to consumers regarding self-medication to help them distinguish between mild and severe disease conditions for which the product would be considered appropriate for use. Swedish drug companies gave information about hydrocortisone drugs in the mass media. The Swedish Board of Health and Welfare developed directives to drug companies giving detailed instructions about the labeling of hydrocortisone. The label indications stated that the drug was only intended for mild eczema, to be used 2 to 3 times a day, and not to be used longer than a week without contacting a physician. Hydrocortisone was not to be used on wounds or near the eyes, and not on children under 2 years of age. Hydrocortisone was available in cream, ointment, powder, solution, and liniment dosage forms. The most suitable dosage form to use depended on the symptoms of the eczema.

It was noted that all drugs in Sweden are distributed through the Apoteksbolaget (a government-owned company for Swedish pharmacies) (Ref. 12). OTC sale of drugs outside of this organization is forbidden. The personnel in the organization were instructed by dermatologists and pharmacists about mild eczema, and written information was distributed to all pharmacy personnel. A pamphlet was developed for customers who wanted to learn more about OTC hydrocortisone. A customer survey (Ref. 12) was undertaken by the Apoteksbolaget and the Department of Social Pharmacy to analyse the effect of OTC use of hydrocortisone 3 months before the October 1, 1983, switch and 1 and 9 months afterwards. The results indicated that misuse of the drug (defined as frequent use) seldom occurred. Six of 104 customers noted skin changes as mild side effects. Opinions of Swedish physicians toward the switch were divided. However, among the dermatologists there was, in general, a positive attitude toward OTC hydrocortisone.

The agency notes that the information regarding Sweden's marketing of 1 percent hydrocortisone without prescription did not include any information on safety and effectiveness considerations. However, the agency

recognizes that Sweden exerts continuing control over the dispensing of OTC drugs by its method of distribution. Also, in addition to labeling instructions, instructions regarding OTC hydrocortisone use were given to individual customers by the government-owned pharmacies. From the information available from Sweden, there appeared to be no problems related to the OTC marketing of 1-percent hydrocortisone products.

Included in the manufacturers' association's submission on foreign marketing was a copy of the Medicines Act Information Letter issued by Great Britain's Department of Health and Social Security (DHHS) to product license holders (Ref. 13). This letter provides detailed information to industry concerning what constitutes an acceptable application. Guidance was provided for companies with an interest in marketing OTC topical hydrocortisone preparations and the following conditions were listed:

(1) Only Hydrocortisone and Hydrocortisone Acetate preparations will be considered;

(2) The maximum strength is 1 percent;

(3) The vehicle must be a cream or ointment;

(4) The suitability of the cream or ointment base and its possible effect on bioavailability of the Hydrocortisone will be considered by the licensing authority. Excipients which significantly increase the bioavailability at the maximum strength will not be suitable;

(5) Evidence of clinical efficacy and/or bioavailability will be required for low strengths or novel formulations;

(6) The only indications are to be irritant dermatitis, contact allergic dermatitis and insect bite reactions. These indications may be worded in advertising and labeling * * *, but the term "eczema" should not be used; "rash" and "dermatitis" would need qualification;

(7) The contraindications should be: use on the eyes/face, anogenital region, broken or infected skin including cold sores, acne and athlete's foot. These contraindications should appear on advertising and labeling * * *;

(8) The product should not be recommended for use on children under 10 years of age without medical supervision;

(9) The product label should carry the following warning: "Do not use in pregnancy without medical advice;"

(10) The dosage instruction should be: "Use sparingly over a small area once/twice a day for a maximum period of one week;"

(11) The labeling must state: "If the condition is not improved, consult your doctor;"

(12) The label should state clearly "Contains Hydrocortisone," except where the product name includes hydrocortisone and appears on the label;

(13) The package size must be between 10 and 15 grams;

(14) Any package insert should be limited to the information required by the Medicines (Leaflets) Regulations 1977. The DHSS will wish, for the time being, to approve all promotional copy.

The agency notes the following differences between FDA's monograph proposals for hydrocortisone (February 8, 1983 and this document) and the practice in Great Britain:

(1) Only cream and ointment dosage forms are allowed in Great Britain; FDA proposes to allow lotion and spray products as well.

(2) Both countries have expressed concern about the effect of bases or vehicles on bioavailability and a need to show clinical effectiveness for low concentrations or unusual formulations. (The agency's conclusions on suitable dosage forms are discussed in Part V. paragraph C. below—*Discussion of Vehicles in Submissions.*)

(3) Great Britain does not propose to allow eczema as an indication, while FDA does.

(4) Great Britain requires advertising and labeling to include contraindications against use on the eyes/face, anogenital region, broken or infected skin, including cold sores, acne, and athlete's foot. FDA proposes to require a label warning to avoid contact with the eyes.

FDA does not include specific contraindications (non-use situations) in the labeling as Great Britain does; FDA handles this by stating the use conditions in the indications for the product. FDA does require when the product is labeled for external genital or feminine itching that it bear a warning stating "Do not use if you have a vaginal discharge. Consult a doctor."

(5) Great Britain recommends that the product not be used on children under 10 years of age without medical supervision; FDA's age limit is not for use on children under 2 years of age.

(6) Great Britain's directions are to use sparingly over a small area 1 or 2 times a day for a maximum period of 1 week; FDA's directions are as follows: Adults and children 2 years of age or older: Apply to affected area not more than 3 or 4 times daily. Children under 2 years of age: consult a physician or doctor. Also, FDA has a warning, "If condition worsens or if symptoms persist for more than 7 days, discontinue use of the product and consult a physician."

As with many drugs, FDA finds the methods of marketing and labeling for OTC hydrocortisone to vary among foreign countries. For example, in Sweden the OTC indication includes "mild eczema," but this term is not allowed in Great Britain. Based upon 10 years of OTC marketing experience of 0.25 to 0.5 percent hydrocortisone in the United States, the agency believes that products containing hydrocortisone at concentrations of 0.25 to 1 percent and hydrocortisone acetate equivalent to 0.25 to 1 percent hydrocortisone may be safely marketed in the United States under existing procedures.

II. Safety

A. Introduction

The agency has reviewed the submitted data as well as the conclusions of the three panels that evaluated the safety of hydrocortisone for OTC use. The agency believes that products containing 0.25 to 1 percent hydrocortisone and hydrocortisone acetate equivalent to 0.25 to 1 percent hydrocortisone are safe for OTC use. Concentrations from 0.25 to 0.5 percent have been marketed OTC in the United States since December 4, 1979, without any major problems occurring, as noted throughout this document.

B. Studies Reviewed by the Panel

The Panel's conclusion that up to 0.5 percent hydrocortisone is safe for OTC use was based in part on its assessment of studies in which concentrations of hydrocortisone of 1 percent or more were used. One of the Panel's conclusions regarding the safety of 0.5 percent hydrocortisone was that percutaneous absorption is minimal and that systemic effects such as those observed after systemic administration are unlikely (44 FR 69768 at 69818). This conclusion is supported by the results of an absorption study conducted by Malkinson (Ref. 14) on the percutaneous absorption of topically applied 2.5-percent hydrocortisone preparations.

Malkinson was unable to demonstrate any absorption of hydrocortisone by normal skin for 5½ to 6 hours after the topical application of a radioactively-labeled 2.5-percent hydrocortisone ointment by using a gas-flow cell that measured the residual radiation at the site of application. Malkinson further reported that there was also no evidence of absorption of the radioactively-labeled 2.5-percent hydrocortisone ointment before or after exposure of the

skin sites to an erythema-producing dose of ultraviolet light. Malkinson stated that it was not surprising that the gas-flow cell was unable to detect any absorption of the ointment by normal skin because the quantitative absorption of this compound is well within the inherent percentage of error of this device. He noted, however, that previous studies had shown that 1 to 2 percent of a topically applied dose of hydrocortisone-4-C^{14} was absorbed by normal skin. Malkinson also demonstrated that skin stripping dramatically increased the amount of absorption of hydrocortisone that could be expected after topical administration.

As additional evidence of the low level of absorption of topically applied hydrocortisone, the Panel cited studies by Smith (Refs. 15 and 16), Fleischmajer (Ref. 17), and Witten, Shapiro, and Silber (Ref. 18). These studies demonstrated no significant systemic effect, i.e., drop in circulating eosinophil count, alteration in plasma or urinary steroids, or changes in blood glucose levels, after the topical application of a preparation containing 2.5 percent hydrocortisone. Smith (Ref. 15) reported no consistent alteration in circulating eosinophil counts after using 6 grams (g) of a 2.5-percent hydrocortisone acetate ointment on eight normal subjects and seven subjects with generalized skin disease. In a subsequent study by Smith (Ref. 16), no significant alteration in urinary 17-ketosteroids or 17-hydroxycorticosteroids as compared to baseline values was demonstrated after the use of 10 g of a 2.5-percent hydrocortisone ointment on eight normal subjects.

Fleischmajer (Ref. 17) reported no clinical side effects directly attributable to treatment and no distinct changes in various laboratory analyses performed during a study of 19 subjects treated twice daily with a 2.5-percent hydrocortisone ointment for periods ranging from 3 to 20 months. The subjects received total doses of hydrocortisone acetate ranging from 8,750 to 95,000 milligrams (mg).

Witten, Shapiro, and Silber (Ref. 18) reported no increase in 17,21-dihydroxy-20-ketosteroid levels in urine and blood after using a 2.5-percent hydrocortisone acetate ointment on six normal subjects and nine subjects with extensive or generalized skin disease. However, the Panel noted that Gemzell, Hard, and Nilzen (Ref. 19) reported an increase in the plasma levels of 17-hydroxycorticosteroids followed by a decrease in circulating eosinophil levels after the application of 200 mg of hydrocortisone in various vehicles to the anterior surface of the body from the neck to the knees in 48 subjects. The authors did not consider these changes significant but suggested that they may be indicative of some general internal effect of hydrocortisone after topical application to the skin.

The Panel conducted a thorough review of the available literature on hydrocortisone and stated that it found no report of the aggravation of cutaneous bacterial, fungal, or viral infection attributable to the topical application of hydrocortisone-containing products (44 FR 69768 at 69817). This review included the 37 efficacy studies cited by the Panel. Of those 37 studies, 31 involved concentrations of hydrocortisone of 1 percent or greater. The Panel did report two cases of secondary infection in patients treated with a 2.5-percent hydrocortisone ointment as part of the Fleischmajer study (Ref. 17). However, Fleischmajer stated that the infections were in areas affected by severe excoriation due to scratching and that the infections promptly cleared after local and systemic antibiotic therapy without any interruption of hydrocortisone therapy.

In another study cited by the Panel, conducted by the Staff of Saint John's Hospital for Skin Diseases and Institute of Dermatology (Ref. 20), the authors reported a few cases of worsening of symptoms due to infection in a study of 708 subjects with various eczemas treated with preparations containing 0.25 to 2.5 percent hydrocortisone or hydrocortisone acetate. The authors concluded, however, that there seemed to be little or no evidence that hydrocortisone ointment positively favors superficial infections.

The Panel also mentioned a multicenter double-blind study by Carpenter et al. (Ref. 21) in which a product containing clioquinol (formerly known as iodochlorhydroxyquin) and 1 percent hydrocortisone was compared to the individual components in the treatment of subjects with acute dermatitis complicated by secondary bacterial or fungal infection. Carpenter et al. found no evidence of the exacerbation of infection in the 68 subjects who received the 1-percent hydrocortisone component.

The Panel's extensive review of the literature revealed no evidence of local changes in the skin such as striae formation or telangiectasia (a vascular lesion formed by the dilation of a group of small blood vessels) directly attributable to the topical application of 1 percent hydrocortisone. The Panel also found there was a low incidence of allergic reactions.

C. Systemic Effects and Risk of Superinfection

The agency has also conducted an extensive review of the data submitted to demonstrate the comparative efficacy of 0.5 and 1 percent hydrocortisone as well as the efficacy studies submitted to the Panel in which concentrations of 1 percent hydrocortisone or more were used. While evaluating the efficacy data, the agency also looked to see whether the studies showed possible systemic effects or a worsening of symptoms due to infection resulting from the application of topical hydrocortisone products. Based on this review, as discussed below, the agency concludes that the likelihood of systemic toxic effects or an increased risk of infection due to the topical application of 1 percent hydrocortisone or hydrocortisone acetate is quite small.

In a study by Robinson, Robinson, and Strahan (Ref. 22) using concentrations of hydrocortisone or hydrocortisone acetate of 0.5, 1.0, and 2.5 percent in 1,655 subjects with various dermatitides, there was no evidence of serious side effects or systemic toxic reactions. A similar conclusion was stated by Robinson and Robinson (Ref. 23) in a followup study using 1 and 2.5 percent hydrocortisone and hydrocortisone acetate concentrations, other steroids, and other salts of hydrocortisone on 2,542 subjects with steroid sensitive dermatitides. Sulzberger and Witten (Ref. 24) treated 252 subjects with selected dermatitides with various ointments containing hydrocortisone 1 and 2.5 percent and reported that the topical application did not produce any clinical evidence of adverse systemic effects. Cahn and Levy (Ref. 25) also reported no manifestation of systemic toxicity in a study that included the application of 1.0 percent hydrocortisone to 58 subjects in the treatment of a variety of common dermatoses.

In a study by Mullins and Hicks (Ref. 26) comparing the effectiveness of 1- and 2.5-percent hydrocortisone preparations in 100 subjects with selected dermatitides, the authors reported that there were no untoward systemic absorption effects in any of the subjects. Kalz, McCorriston, and Prichard (Ref. 27) observed 581 subjects with multiple dermatitides treated with preparations containing 1 to 2.5 percent hydrocortisone and noted no evidence of systemic effects due to the absorption of hydrocortisone. However, they observed the development of follicular pustules and boils in the areas treated in four of the patients included in their

study. Polano (Ref. 28) also reported no untoward side reactions in a study comparing 1 percent hydrocortisone to other treatments in 245 subjects with a variety of dermatitides.

In a study involving 259 subjects with various dermatitides, Howell (Ref. 29) reported no evidence of percutaneous absorption from a 1- or 2.5-percent hydrocortisone ointment. Howell also noted that six subjects with chronic allergic (atopic) eczema included in the study had practically generalized involvement and that the ointment was applied over extensive areas of the body for as long as 2 months without any untoward effect. Portnoy (Ref. 30) noted no cutaneous or systemic reactions in any of 129 subjects with pruritus ani, pruritus vulvae, infantile eczema, contact dermatitis, and flexural prurigo who were treated with 0.1 percent 9α-fluorohydrocortisone or 1-percent hydrocortisone ointment. Warin (Ref. 31) reported no tendency to secondary infection or systemic effects in treating 40 infants and children suffering from infantile eczema with 1 or 2.5 percent hydrocortisone acetate.

Infectious complications occurred in 9 (2.23 percent) out of the 402 subjects with chronic dermatitides who were treated with 1.0 and 2.5 percent hydrocortisone or hydrocortisone acetate in a study by Welsh and Ede (Ref. 32). However, these secondary infections were easily controlled with topical antibiotics. The authors considered this a low incidence of secondary infection and concluded that based on these results and the known sensitizing properties of antibiotics, that it is inadvisable to use hydrocortisone with a topical antibiotic as a regular therapeutic approach. In a study of 1 and 2.5 percent hydrocortisone by Russell et al. (Ref. 33), one out of the 132 subjects developed a secondary infection. This subject, who was being treated for otitis externa, experienced an increase in swelling and exudation of the ears shortly after treatment was begun with the hydrocortisone ointment. The patient's eyes also became swollen. Culture revealed *Staphylococcus pyogenes, Streptococcus haemolyticus,* and *Pseudomonas pyocyanea.* Patch tests with hydrocortisone and the vehicle were negative.

The observations of these investigators indicate that even under the exaggerated conditions of use (relative to OTC use) found in these studies, the risk of systemic effects or an increased incidence of secondary infections following the use of topical 1 percent hydrocortisone or hydrocortisone acetate is minimal. No systemic effects were noted in any of these studies. While some cases of secondary infection have been reported, they do not appear to be of a serious nature. The agency believes that these potential risks would be further diminished under the proposed label limitations of OTC use, i.e., a 7-day maximum treatment period on minor skin irritations with a warning to discontinue use of the product and consult a doctor if the condition worsens, or if symptoms persist for more than 7 days or clear up and occur again within a few days. These warnings were proposed in § 348.50(c)(1)(iii) of the tentative final monograph for OTC external analgesic drug products (47 FR 5852 at 5868).

D. Sensitization and Irritation Potential of Hydrocortisone

Few cases of sensitization or irritation due to the topical application of hydrocortisone or hydrocortisone acetate have been reported in clinical studies involving over 6,000 subjects (Refs. 20, 22, 24, 25, 26, 27, and 32 through 40). Rather, patch testing, when done on subjects who had exacerbation of symptoms during treatment, showed reactions for the most part to be due to local irritations from ingredients in the vehicle or base (e.g., lanolin), and not to hydrocortisone or hydrocortisone acetate ([Refs. 20, 22, 32, 33, 37, and 38). However, there have been some verified reports of allergic sensitivity to hydrocortisone or hydrocortisone acetate.

Coskey (Ref. 41) reported two cases of allergic reactions in subjects with otitis externa whose conditions were aggravated by the application of topically applied preparations containing 1 percent hydrocortisone. Patch tests conducted on these subjects revealed a sensitivity to hydrocortisone. Coskey stated that it was difficult to explain why one subject was sensitive to hydrocortisone alcohol but not to hydrocortisone acetate. Coskey theorized that the subjects may have been sensitive to one of the precursors of hydrocortisone (e.g., 21-diol acetate), but this could not be determined because patch tests for these substances were not available. Edwards and Rudner (Ref. 42) reported a case that was interpreted as an example of pure hydrocortisone sensitivity in an atopic subject treated for a weeping eczematous dermatitis of the feet with a 1-percent hydrocortisone cream. A patch test ruled out all components of the suspected product except for the pure hydrocortisone powder. Kooij (Ref. 43) reported a case of sensitivity to hydrocortisone in a subject with weeping eczema of the face and hands whose condition worsened after treatment with a 1-percent hydrocortisone ointment. Positive patch test results were obtained with several brands of hydrocortisone preparations (ranging from 0.5- to 1.5-percent concentration) and to a pure solution of 6 percent hydrocortisone succinate in water. Kooij concluded that, based on these results, it could be assumed that this was a case of hypersensitivity to a pure hydrocortisone compound.

Alani and Alani (Ref. 44) performed a series of routine patch tests to study the incidence of cortisone and other corticosteroid sensitivity. Tests were performed on 1,835 subjects with contact dermatitis. A retrieval search for subjects with allergic contact dermatitis suspected of being sensitive to steroid creams was also performed. The 17 subjects obtained from the retrieval search were also tested with the routine patch test series. Included in the test were purified preparations of hydrocortisone and hydrocortisone acetate, two proprietary preparations, two mixtures of hydrocortisone and hydrocortisone acetate by two different manufacturers, various brands of hydrocortisone and hydrocortisone acetate, and two brands of prednisone. Concentrations of hydrocortisone and hydrocortisone acetate used in the patch tests were 10, 15, and 25 percent. All subjects who showed sensitivity by patch testing to cortiscosteroids were subsequently patch-tested with supplemental patch tests that included previously-used topical steroids and all other constituents of the suspected offending steroid cream. The consecutive routine patch test revealed six subjects (0.3 percent) who gave positive reactions to two mixtures of hydrocortisone and hydrocortisone acetate of two different brands. Alani and Alani concluded that based on the negative reactions among 1,835 consecutive subjects, irritant reactions are rare. However, they stated that they expected the incidence of corticosteroid sensitivity to increase due to the tendency of higher concentrations of steroids in proprietary preparations. The incidence of sensitivity reactions in this study from Sweden is apparently higher than the incidence observed in the clinical studies discussed below. This may in part be due to differences in European and United States drug product formulations and the lack of patch testing with the chemical precursor in the synthesis of hydrocortisone acetate, 21-diol acetate. For example, in a European study, Church (Ref. 45) demonstrated that five

cases of apparent sensitivity to an ointment containing hydrocortisone acetate were actually due to 21-diol acetate that was present in the product in small amounts as a contaminant, apparently left over from the manufacturing process.

In the clinical study conducted by Robinson, Robinson, and Strahan (Ref. 22) involving 1,655 subjects, no serious cutaneous reactions were observed. The majority of the local reactions noted was due to local irritative phenomena and not primarily to sensitization. Further, the more complicated the product base was, the higher the percentage of reactions. Local irritations were noted in 81 individuals, who were patch tested with the vehicle minus the steroid. In each instance, the irritation was due to the vehicle in which the active ingredient was dispensed. Two subjects with acne vulgaris developed numerous new follicular lesions following the application of 1.0-percent hydrocortisone acetate greaseless cream, but no other reactions that could be attributed to the local application of the steriod occurred in any of the subjects. Two subjects, treated with an oily base containing lanolin, developed erythema at the site of application. Patch tests on both of these individuals were positive for lanolin.

In another study by Robinson and Robinson (Ref. 34) involving 418 subjects treated with concentrations of 0.5, 1.0, and 2.5 percent hydrocortisone and hydrocortisone acetate in several different vehicles, two subjects with acne vulgaris developed numerous new lesions after the application of a 1.0-percent hydrocortisone acetate greaseless cream. The authors stated that this was the only adverse reaction that could be attributed to the primary ingredient in the cream. Thirty-eight subjects (treated with three different hydrocortisone preparations) developed mild adverse reactions as evidenced by a moderate increase in erythema and itching. However, the authors concluded that any evidence of local sensitivity was invariably caused by the base in which the drug was dispensed.

Rattner (Ref. 35) reported in a study of 1,200 subjects with various dermatological conditions, who were treated with concentrations of hydrocortisone or hydrocortisone acetate of 0.5, 1, and 2.5 percent, that neither the acetate nor the free alcohol proved irritating and that both caused only a localized action. In another report (Ref. 20), 22 (approximately 3 percent) of the 708 subjects treated with hydrocortisone or hydrocortisone acetate experienced a worsening of their eczematous lesions. Patch testing revealed no hypersensitivity to hydrocortisone, but occasional intolerance to all available hydrocortisone products was demonstrated.

Malkinson and Wells (Ref. 36) reported that irritation occurred in 4 of 71 subjects with various superficial inflammatory dermatoses who were treated with an ointment containing 2.5 percent hydrocortisone acetate. However, the authors further reported that no evidence of allergic sensitivity to hydrocortisone was demonstrated. Russell et al. (Ref. 33) reported no cases of sensitization in 132 subjects treated for various dermatological conditions with an ointment containing hydocortisone 1 or 2.5 percent or the ointment vehicle. Three subjects abandoned treatment due to a worsening of symptoms. Two of these were either sensitive to the vehicle or one of its constituents, and the third abandoned treatment apparently in response to a secondary infection. One subject who complained that the ointment "burned" was using the vehicle. Another subject complained of a fresh outcrop of vesicles after applying the hydrocortisone ointment for three days. Patch tests conducted with the hydrocortisone ointment and the vehicle were negative. However, when patch testing was carried out with the separate constituents of the vehicle, a positive reaction was obtained to propylene glycol.

Rein (Ref. 37) reported that 4 of 131 subjects experienced a flare-up of their dermatitides after the use of hydrocortisone acetate cintment. Patch tests on these subjects conducted with the free alcohol, the acetate, and the base all gave negative reactions.

Friedlaender and Friedlaender (Ref. 38) reported that the dermatitis became worse in 9 (5.6 percent) of 159 subjects following the use of one of various hydrocortisone or hydrocortisone acetate ointments or hydrocortisone acetate/neomycin combinations. Sensitization to hydrocortisone, hydrocortisone acetate, or neomycin could not be demonstratred in any of these subjects. Six subjects were felt to be sensitive to the oinment base used as determined by patch tests or repeated applications of the base ointment to areas of the dermatitis and uninvolved skin. Three subjects were determined to be sensitive to the wool-fat base. Two subjects were felt to be sensitive to petrolatum, while two subjects appeared to be irritated due to the use of an ointment during an acute phase of their dermatitis. One subject showed aggravation and progression of poison ivy lesions after extensive local application of hydrocortisone in both types of ointment bases. Patch tests performed several weeks after the complete subsidence of the dermatitis failed to reveal any evidence of specific sensitization. Further, the subject was given the ointments to rub into the skin daily for several weeks and no irritation resulted. The authors felt that "the aggravation noted was due to primary irritation by an ointment in an acute phase of a dermatitis which ordinarily would be treated by bland local therapy such as compresses, colloid baths, and shake lotions." The cause of the aggravation of symptoms was not determined in one subject.

Welsh and Ede (Ref. 32) reported that 3 of 402 subjects with chronic dermatitides had reactions to 1.0 or 2.5 percent hydrocortisone acetate. However, in subsequent patch tests, the reactions proved to be due to the ointment base and not to hydrocortisone. Kalz, McCorriston, and Prichard (Ref. 27) reported 12 instances of irritation or exacerbation of the skin condition treated in 581 subjects. The ointment base rather than the hydrocortisone acetate (1 to 2.5 percent) was found to be responsible in all cases. The carbowax base was the offending agent in most instances, either because of its drying properties or allergic sensitization. Petrolatum and oily cold creams were not well tolerated in some cases because of their oily and heavy consistency.

Brodthagen (Ref. 39) reported several instances of exacerbation of symptoms in 195 subjects treated with a 2-percent hydrocortisone acetate ointment. However, this exacerbation generally subsided under continued treatment. In three of these subjects, an eczema test was performed with the ointment with negative results. Sulzberger (Ref. 40), in a symmetrical pared comparison of 9α-fluorohydrocortisone to hydrocortisone in the treatment of 82 subjects with assorted dermatitides, reported that no instances of allergic sensitization were observed following the topical application of any of the hydrocortisone derivatives. Sulzberger and Witten (Ref. 24) reported no cases of allergic sensitization directly attributable to the 1.0 and 2.5 percent hydrocortisone acetate or the hydrocortisone free alcohol ointments used to treat 252 subjects. The authors reported that they had not observed any instances of allergic sensitization even after prolonged use and predicted that the sensitization index for these ingredients would be very low. Mullins and Hicks

(Ref. 26) similarly reported no evidence of primary irritation or sensitization during treatment of 100 subjects with 1 and 2.5 percent hydrocortisone acetate. Cahn and Levy (Ref. 25) reported that there were no manifestations of local hypersensitivity in 58 subjects who applied 1.0 percent hydrocortisone to various dermatoses.

E. Local Effects of Hydrocortisone

Localized dermal effects such as skin atrophy, striae, or telangiectasia that have been observed following topical use of more potent fluorinated steroids have rarely been reported following topical application of a hydrocortisone. In addition to the case report of a woman who developed atrophy with telangiectasia of the eyelid skin following topical application of a hydrocortisone preparation to her eyelids for "several years" as a cosmetic (Ref. 46), which was cited by the Panel (44 FR 69768 at 69817), the agency has identified only one other similar report in the literature. Guin (Ref. 47) reported atrophy of the skin and telangiectasia of the eyelids in two women who had used preparations containing 1 percent hydrocortisone for periods of 12 and 4 months, respectively. The agency is not aware of any studies or case reports of skin atrophy occurring with hydrocortisone under conditions of OTC use as proposed in the tentative final monograph for OTC external analgesic drug products (48 FR 5852 at 5868).

Smith, Wehr, and Chalker (Ref. 48) used a bioassay method to evaluate the adverse effects (including skin atrophy and telangiectasia) of nine topically applied corticosteroids, which included 1.0-percent hydrocortisone cream. A topical application of 0.1 g of the cream was applied to a shaved midposterior lateral area of the back of young Sprague-Dawley rats for 28 days. The animals were weighed twice weekly and evaluated for telangiectasia. On day 28 of the study, the animals were sacrificed and the skin thickness was determined by lifting a skin fold and measuring the double skin-fold thickness with a micrometer with a potential accuracy of 0.0001 inch. The authors found no evidence of telangiectasia in any of the rats treated with the 1.0-percent hydrocortisone, while the other eight corticosteroids produced mild to severe telangiectasia. The authors concluded that the weight gain correlated well with skin thickness and that 1.0 percent hydrocortisone (and 0.1 percent betamethasone valerate) had the least effects on weight gain and double skin thickness as compared with controls.

Other data in humans, in which sophisticated techniques were used to measure changes in skin thickness, support the safety of 1 percent hydrocortisone for OTC use. James, Black, and Sparkes (Ref. 49) studied the localized dermal effects of 4 test steroids in 20 normal adult males 25 to 40 years of age. The test steroids were 0.0125-percent flurandrenolone cream, 0.05-percent clobetasone butyrate cream, 0.1-percent hydrocortisone 17-butyrate cream, and 1-percent hydrocortisone cream. The control steroid used was 0.025-percent fluocinolone acetonide cream. Volunteers were asked to rub a standard amount of the control and test steroids into an outline area of the middle one-third of the radial aspect of contralateral forearms twice daily for 3 months. Radiographs of the forearm skin were taken before application and at monthly intervals for 3 months. The authors reported that at 3 months significant atrophy was seen in 14 of 19 subjects using fluocinolone acetonide, 3 of the 5 subjects using clobetasone butyrate, all of the 5 subjects using hydrocortisone 17-butyrate, 1 of 4 subjects using flurandrenolone, and none of the 5 subjects using 1-percent hydrocortisone cream.

A double-blind, half-side study by Black, Platt, and Mugglestone (Ref. 50) compared dermal atrophy in 29 healthy male volunteers using various steroid preparations: 0.75 percent fluocortin butylester, 0.05 percent clobetasone butyrate, 1 percent hydrocortisone acetate, and the base placebo creams. Each volunteer was instructed to apply a 1 centimeter (cm) length of the cream being used to a clearly defined area on each forearm twice daily for a period of 8 weeks. The skin thickness at the site of application was determined by a modified radiographic technique immediately prior to the first application of the creams and again after the eighth week of application. Clinically significant skin thinning occurred in 3 of the 10 subjects treated with clobetasone butyrate, and atrophy of a marginal significance occurred in 1 of the 29 subjects treated with fluocortin butylester. Only 1 of 10 subjects treated with a 1-percent hydrocortisone cream experienced a statistically significant increase in skin thickness. However, the authors judged this increase not to be clinically significant. The remaining nine subjects treated with 1-percent hydrocortisone cream had no significant difference between the initial and post-treatment skin thickness.

Snyder and Greenberg (Ref. 51) also used a double-blind comparative methodology to study the effects of chronic usage of commercially prepared formulations of a 1-percent hydrocortisone cream, a 0.1-percent triamcinolone acetonide cream, and a placebo cream. Five dermatologically normal male and female volunteers were randomly assigned coded creams and instructed to apply each cream to an appropriately demarcated area on the volar forearm three times a day. A small amount of each cream was rubbed into an area of approximately 8 square centimeters (cm^2) and the excess was removed by blotting. No more than two creams were applied to each forearm. Daily treatment continued without exception for 12 weeks at which time all treatments ceased. Skin thickness of the test area was measured by soft tissue X-ray techniques. After approximately 2 months of treatment with the 0.1-percent triamcinolone acetonide cream, all subjects showed clinical signs of skin atrophy. At no time during the 12-week treatment period did the 1-percent hydrocortisone or placebo treated sites show any clinical signs of atrophy. The average percent decreases in skin thickness measured after 8 weeks of treatment were 6 percent for the placebo and hydrocortisone test sites and 17.1 percent for the triamcinolone acetonide cream test sites. The authors reported that, based on a matched-pair comparison test, the difference in skin thickness between triamcinolone acetonide and 1-percent hydrocortisone treatment was significant at $0.1 > p > 0.05$ and that there was no significant difference in skin thickness between skin treated with hydrocortisone and placebo cream. During the first week after cessation of treatment, the clinical appearance of the skin began to improve and by 1 month all treated areas had essentially returned to pretreatment thickness.

In a double-blind controlled investigation by Tan, Marks, and Payne (Ref. 52), 48 healthy adult male and female volunteers were randomly assigned to treatments of 2 of 6 preparations (1 for each forearm). The treatments were two of the following applied to the flexor aspect of the forearm twice a day: The cream base, a 1-percent hydrocortisone cream, a 0.1-percent hydrocortisone 17-butyrate cream, a 0.05-percent clobetasone butyrate cream, a 0.1-percent betamethasone 17-valerate cream, and a 0.05-percent clobetasol propionate cream. A one centimeter extrusion of the cream was applied to a defined area measuring 10 × 5 cm and the area was not washed for at least 1 hour after application. The total amount of cream applied to each area over the 6-week

treatment period was approximately 30 g.

Both xeroradiographic and pulsed ultrasound techniques were used to measure skin thickness before and after 6 weeks of treatment. Measurements using the ultrasound technique were also made at days 2, 4–5, 8–9, 14–16, 28–30, and 42–44, and at 4 weeks after cessation of treatment. Dermal thinning of 4 to 5 percent could be detected by ultrasound measurement as early as 2 days after treatment with betamethasone 17-valerate and clobetasol propionate. Dermal thinning in the hydrocortisone group was 13 percent as measured by ultrasound and 7 to 8 percent measured by the radiographic technique. The placebo group showed 9 percent dermal thinning using ultrasound measurements and 4 percent using the radiographic technique. Overall, the degree of dermal thinning was greater as measured by the ultrasound technique than when measured by the radiographic technique. The authors found that an analysis of variance comparing the dermal thinning induced by the 1-percent hydrocortisone cream versus the base from data derived from both techniques did not reach the nominal $p=0.05$ level of statistical significance. Recovery from dermal thinning, to 91 to 96 percent of the pretreatment values, was apparent in all treatment groups 4 weeks after cessation of therapy.

Kirby and Munro (Ref. 53) studied the effects on mice and humans of several different steroid preparations commercially available in the United Kingdom. Included in both segments of the study was 0.1 percent hydrocortisone incorporated in a water miscible base. In the human portion of the study, 0.05 milliliter (mL) of the test preparation was applied to a well defined area of the forearm of two groups (Groups I and II) of normal adult volunteers and covered by an occlusive dressing. In Group I, the site of application was not varied. In Group II, the site of application on the forearm was varied. Changing sites did not produce statistically significant differences between right or left arm, proximal or distal placement on the same side.

Skin-fold thickness measurements were made at points on the flexor of the forearm before the initial application of the test preparations and repeated at 7-day intervals for 2 weeks. The dressings were renewed after each of the measurements taken at weeks one and two. After one week all compounds tested produced thinning skin in both groups. Two week measurements showed a further decrease in skin thickness on the corticosteroid treated sites in Group I while the two week measurements in Group II showed a varied response, with some preparations (including 0.1 percent hydrocortisone) showing an increase in thickness beyond the first week's readings. Among the steroids tested, the 0.1-percent hydrocortisone preparation produced less thinning than any of the other steroid preparations tested in the two groups, but more thinning than the placebo. However, it is unclear from the study to what extent the base for the 0.1-percent hydrocortisone product resembled the placebo used in the study. Because other investigators (Refs. 51 and 52) have demonstrated that the base can produce dermal thinning of its own that is comparable to that demonstrated by the 0.1-percent hydrocortisone in this study, the conclusion that the observed dermal thinning is attributable to the hydrocortisone content of the preparation is in doubt. Recovery of thinning was noted within two weeks with three of the preparations tested, including the 0.1-percent hydrocortisone preparation.

In summary, the studies conducted on humans on the effects of these corticosteroids on skin thickness show that prolonged use without occlusion of 1 percent hydrocortisone for periods of up to 11 weeks does not produce changes in skin thickness that are statistically or clinically significant from the control base. Moreover, these studies demonstrate that what changes do occur readily reverse themselves after cessation of treatment. These findings also indicate that the occasional case reports of skin atrophy that have appeared in the literature result from the use of hydrocortisone preparations on susceptible areas of the body well in excess of the recommended period of use in the proposed OTC labeling for products containing this ingredient. Based on the above studies, the agency believes that the risk of skin atrophy, striae, and telangiectasia is small within the recommended period of use being proposed for OTC drug products containing up to 1 percent hydrocortisone.

F. Rebound Potential

The Miscellaneous External Panel in its review of hydrocortisone stated that there is a rebound effect, i.e., a return of symptoms more severe than those experienced prior to treatment, when therapy with fluorinated corticosteroids is gradually discontinued (47 FR 54640 at 54675). The Panel further stated that it was not known whether this effect may occur with hydrocortisone preparations of higher than 0.5 percent. However, a review of the published literature reveals only descriptions of relapse of symptoms upon discontinuance of hydrocortisone therapy at concentrations greater than 0.5 percent and no tendency for rebound.

Heilesen, Kristjansen, and Reymann (Ref. 54) reported that relapse occurred in the majority of 25 subjects suffering from anogenital eczema when withdrawal of 1-percent hydrocortisone therapy was attempted. However, the authors pointed out that several of these subjects had symptoms for 10 to 15 years before the study and had been resistant to the dermatologic treatments generally employed. Relapse was also reported in one subject with nummular eczema. Treatment of this subject with hydrocortisone produced a rapid regression of symptoms that was followed by a prompt relapse of symptoms upon transition to therapy with the ointment base alone. However, the authors further reported several cases in which no relapse occurred. One subject with neurodermatitis of 10 years standing was able to do without hydrocortisone treatment for a month without experiencing a relapse, and two other subjects with neurodermatitis needed only to apply the hydrocortisone ointment at intervals of several days.

In their study of 1,655 patients, Robinson, Robinson, and Strahan (Ref. 22) noted that in most instances continued applications of hydrocortisone free alcohol and hydrocortisone acetate in concentrations of 0.5, 1.0, and 2.5 percent were necessary to maintain the relief of symptoms of atopic dermatitis, neurodermatitis, allergic contact dermatitis, stasis dermatitis, and pruritus ani and vulvae. Relapses occurred when the applications were discontinued. However, the authors also stated that when the eruption or symptoms had completely subsided it was possible in the majority of subjects to reduce the frequency of applications to once daily or once every other day.

The staff of Saint John's Hospital (Ref. 20) reported that complete clearing of symptoms without relapse was uncommon (6 percent) in the 100 patients treated for atopic eczema with concentrations of hydrocortisone and hydrocortisone acetate ranging from 0.25 to 2.5 percent. The authors further reported that in 86 subjects suffering from discoid eczema, relapse occurred regularly on withdrawal of hydrocortisone therapy. Kalz, McCorriston, and Prichard (Ref. 27) similarly reported that short remissions were induced in many subjects treated

for atopic dermatitis with a 1- or 2.5-percent hydrocortisone ointment, but that some relapses occurred after several weeks. In some instances, the relapses were not well controlled by the 1-percent hydrocortisone ointment and the 2.5-percent ointment was required. Brodthagen (Ref. 39) also observed relapses during and after treatment of subjects suffering from a variety of dermatitides with a 2-percent hydrocortisone acetate ointment. However, Brodthagen reported that the relapses were rarely as severe as the original eruptions and, as might be expected, the frequency of relapse is the highest after the shortest period of treatment.

The above data demonstrate that hydrocortisone and hydrocortisone acetate provide only a temporary control of symptoms for certain types of skin conditions and that a relapse of symptoms can occur when treatment with concentrations of 0.5 percent or greater of these ingredients is stopped. However, the data further demonstrate that in those cases where hydrocortisone therapy does not effect a cure but is only used to provide symptomatic relief, no rebound of symptoms upon cessation of therapy would be expected. With regard to the possibility of a relapse of symptoms when the use of OTC drug products containing hydrocortisone or hydrocortisone acetate is stopped, the agency believes that the risk to consumers is minimal. The studies where relapse was reported involved subjects with dermatological disorders more severe than the indications proposed for hydrocortisone-containing products in the tentative final monograph for OTC external analgesic drug products (48 FR 5852 at 5868). Moreover, the agency believes that consumers who experience a relapse of symptoms are provided adequate guidance by the proposed warning in § 348.50(b)(7), which warns against further use of these products without first consulting a physician when symptoms clear up and occur again in a few days.

G. Adverse Drug Reactions

The agency has reviewed a summary listing of adverse drug reactions reported for single entity hydrocortisone drug products (both prescription and OTC) to its Spontaneous Reporting System for the years 1970 through 1989 (Ref. 55). This summary listing includes 724 reports of adverse drug reactions to these products. Of these reports, 207 relate to adverse drug reactions associated with the topical use of hydrocortisone or hydrocortisone acetate containing drug products in varying concentrations from 0.25 to 2.5 percent. Virtually all of the reported reactions related to the use of these products are of a topical nature, with contact dermatitis (61 reports), allergic reaction (48 reports), rash (33 reports), application site reaction (23 reports), and pain and pruritus (29 reports) being the most frequently reported reactions. A review of the corresponding case reports for these reactions (Ref. 56) indicates that the reactions reported for drug products containing 0.5 and 1 percent hydrocortisone or hydrocortisone acetate are similar and that use of the higher 1-percent concentration does not appear to result in more severe reactions. None of these reports indicate that disability or death occurred as an outcome to these reactions.

Two case reports (Refs. 57 and 58) indicated hospitalization occurred as an outcome of reported reactions associated with the use of an OTC drug product containing 0.5 percent hydrocortisone acetate. Although not indicated by the case report for the reaction (Ref. 59), the agency was subsequently informed of a third hospitalization associated with the use of the same OTC hydrocortisone product (Ref. 60). However, the agency notes that in each case the product was not used according to the indications currently proposed in § 348.50(b)(3) (i) and (ii) of the tentative final monograph for OTC external analgesic drug products (48 FR 5852 at 5868), which states that these products are indicated for the temporary relief of itching associated with minor skin irritations and rashes due to minor conditions such as eczema, insect bites, or poison ivy. Two of the reports (Refs. 57 and 58) involved an exacerbation of an existing infection while the third report (Refs. 59 and 60) involved an incidence of bullious erythema multiforme associated with the use of the hydrocortisone product under a band aid on a scratch and a blister. The physician reporting this reaction commented that the precise etiology of his patient's rash was never determined and that the patient had reported a preceding respiratory reaction, which could not be ruled out as the cause of the rash (Ref. 59.)

The agency notes that the majority of the reported reactions appears to be the result of irritancy or sensitivity resulting from use of the products. In a few cases, the cause of the reaction is confirmed by patch testing with the individual components of the product. In the majority of the instances where patch tests were performed using the components of the product, sensitivity or irritation due to one or more of the excipients included in the product was demonstrated (Ref. 61). While no conclusions regarding the incidence of sensitivity or irritation to hydrocortisone or hydrocortisone acetate among these reported reactions can be made because of the lack of definitive patch tests in the majority of these reports, the agency believes that the information derived from the patch tests that were performed supports the occurrence of confirmed allergic sensitivity reactions to hydrocortisone or hydrocortisone acetate, at least for some individuals, that was observed by the agency in its safety evaluation of clinical studies of the drug. (See part II. paragraph D. above—*Sensitization and Irritation Potential of Hydrocortisone.*)

The adverse drug reaction data for single entity hydrocortisone or hydrocortisone acetate containing products provided by manufacturers of these drug products from their own adverse drug reaction files (Refs. 3 and 4) to support the safety of the OTC use of these ingredients describe the same type of topical reactions as disclosed by the agency's Spontaneous Reporting System. Some additional reports are included in the data provided by the manufacturers. However, none of these reports provide sufficient detail to permit a definitive evaluation of the cause of these reactions.

Not all of the adverse reaction data provided by manufacturers relate to the safety of 1 percent hydrocortisone or hydrocortisone products. One manufacturer reported that 67.7 percent of the reports received by the company for its 0.5 percent hydrocortisone acetate products from December 10, 1979, through December 31, 1987, were for a lack of effectiveness (Ref. 4).

The agency finds that the adverse drug reaction data in its Spontaneous Reporting System and reported by the manufacturers of these products are consistent and reflective of the adverse drug reaction profile described in the clinical studies discussed above. (See part II. paragraphs C. through E. above.) As in the clinical studies, the majority of the adverse drug reactions reported were minor topical reactions. With the exception of a single foreign report of hypokalemia (Ref. 62), there is no evidence of the putative systemic effects cited by the Panel that can occur when hydrocortisone is administered orally or parenterally, i.e., suppression of the adrenal axis (44 FR 69768 at 69818). Further, the report of hypokalemia is questionable because the route of

administration of the hydrocortisone treatment is not specified.

The adverse drug reaction data include one report of secondary infection (Ref. 63), one report of withdrawal symptoms (Ref. 64), and two reports of skin atrophy (Ref. 65) associated with the topical use of hydrocortisone or hydrocortisone acetate drug products. The agency finds the incidence of these reports and the accounts of hospitalization to be a very small percentage of the total number of reported reactions, considering the widespread use of these products.

Therefore, based on the safety data obtained from the thousands of subjects who participated in the clinical studies of the safety and effectiveness of these products and the supportive evidence of the subsequent adverse drug reaction experience for these products reported to the manufacturers and the agency, the agency proposes that hydrocortisone or hydrocortisone acetate at a concentration of 1 percent can be safely used topically as an OTC drug product for the indications discussed above.

III. Effectiveness

A. Introduction

After reviewing the data and other information relating to the effectiveness of 1 percent hydrocortisone provided in the citizen petition (Ref. 3) and in the submission by the manufacturers' association (Ref. 4), the agency concludes that they demonstrate that 1 percent hydrocortisone is a more effective concentration than 0.5 percent for OTC use to provide relief in many pruritic conditions. Based on the view that OTC drug products should contain the lowest effective dosage, the Panel recommended 0.25 to 0.5 percent as the effective OTC concentration for hydrocortisone and hydrocortisone acetate equivalent to hydrocortisone. However, the agency notes that the majority of the controlled studies cited by the Panel as demonstrating effectiveness for topical hydrocortisone involved 1 percent hydrocortisone, and in several studies 2.5 percent was the concentration used (44 FR 69768 at 69822).

The effectiveness of concentrations of hydrocortisone and hydrocortisone acetate above 0.5 percent was evaluated as part of the agency's Drug Efficacy Study Implementation (DESI) review of prescription topical corticosteroid drugs. In the Federal Register of April 1, 1971 (36 FR 7982), based on reports received from the National Academy of Sciences-National Research Council (NAS-NRC), the agency stated conditions under which 0.5- to 2.5-percent hydrocortisone preparations (ointment, cream, lotion, aerosol spray, or any other form suitable for topical application) were effective for symptomatic relief and adjunctive management of certain dermatoses. Based on the NAS-NRC evaluation and subsequent data that have been submitted to the agency and reviewed by the Panel and FDA, the agency has determined that substantial data exist that demonstrate the effectiveness of 1 percent hydrocortisone for various dermatitides, eczemas, and other indications that are discussed below.

B. A Low Potency Steroid

Several reports show that hydrocortisone (alcohol or acetate) is a low potency steroid. As a result of the chemical synthesis of more potent topical steroids, a ranking system for relative potency was developed. Miller and Munro (Ref. 66) described one method (the vasoconstrictor test) for assessing topical corticosteroid activity. Effectiveness is judged by the drug's ability to cause skin blanching under occlusion. By this assay method, the relative potency is a composite of several of the corticosteroid's properties: its ability to penetrate the skin barrier after release from the vehicle, its intrinsic activity at the receptor, and its rate of clearance from the site. There is usually a strong correlation between clinical and assay results, but the evidence does not suggest that increased absorption is responsible for the increased clinical activity of the more potent compounds. The clinical potency of hydrocortisone (alcohol and acetate) 0.1 to 1.0 percent was rated as "mild" (lowest potency) by this assay, while beclomethasone dipropionate 0.5 percent was ranked as "very potent," hydrocortisone butyrate 0.1 percent as "potent," and fluocinolone acetonide 0.01 percent as "moderately potent."

Sneddon (Ref. 67) divided topical corticosteroids into four grades of potency and classified hydrocortisone 1 percent as "weak" (grade IV-lowest rating). Stoughton (Ref. 68) used vasoconstriction bioassay techniques to compare the relative effectiveness of various corticosteroids applied topically in controlled clinical studies. Hydrocortisone acetate 1.0 percent had a comparative effectiveness of 1, versus 10 for flurandrenalone acetonide 0.05 percent, 100 for triamcinolone acetonide 0.1 percent, and 360 for betamethasone valerate 0.1 percent.

Barry and Woodford (Ref. 69) evaluated the comparative bioavailability of 30 topical corticosteroid creams and gels for vasoconstriction using an occluded blanching test. The method differed from other vasoconstriction assays in that a more sensitive estimation of pallor and more reading times were employed in order to determine the complete blanching profile of the preparation. Hydrocortisone and its acetate at a 1-percent concentration were ranked 29th (hydrocortisone) and 30th (acetate) with area under the blanching curve values of 180 and 167, respectively, when occluded. Comparatively, the highest ranked drug, with a value of 2,800 occluded, was clobetasol propionate 0.05 percent. The authors stated that hydrocortisone and its acetate are recognized as being less potent than newer steroids and were at the bottom of the classification table of preparations. As was also noted in the Miller and Munro study (Ref. 66), the authors thought the results indirectly suggest that the ranking of proprietary corticosteroid preparations based on the skin blanching tests may reflect their relative clinical efficacy.

Barry and Woodford (Ref. 70) did a similar study with 31 corticosteroid ointments. The concentration for hydrocortisone and hydrocortisone acetate was 0.1 percent. Hydrocortisone acetate ranked 30th and hydrocortisone 31st with values of 368 and 175, respectively, when occluded. Fluocinolone acetonide 0.025 percent ranked first with a value of 2,750 occluded, and 2,530 nonoccluded. Although hydrocortisone and hydrocortisone acetate ointments were tested at a lower concentration (0.1 percent) than the creams (1 percent) used in the first study (Ref. 69), the values obtained were higher, especially for hydrocortisone acetate. The authors did not provide an explanation of these results. However, it was indicated that the area under the curve values in the tests were often higher for ointments probably because of the occlusive effect of the ointment vehicle. In both studies, the hydrocortisone and hydrocortisone acetate ointment and cream were ranked last of all the products tested, demonstrating that hydrocortisone is a low potency steroid.

Cahn and Levy (Ref. 25) used hydrocortisone 1.0 percent as the reference standard in evaluating the relative effectiveness of several topical corticosteroids. The investigators noted that hydrocortisone had received the widest recognition and most extensive use in the treatment of inflammatory dermatoses and had been considered for years as the benchmark against which the effectiveness of new steroids was measured.

The Medical Letter (Ref. 71) has stated that topical corticosteroids are

effective in the treatment of a variety of common skin disorders including seborrheic dermatitis, neurodermatitis, psoriasis, atopic determatitis, and anogenital pruritis, and, in general, the fluorinated topical corticosteroids are more effective than other preparations. However, it was indicated that many disorders respond equally well to the less potent and less expensive steroids such as hydrocortisone. Topical steroid preparations were arranged in a chart roughly according to strength. Hydrocortisone 0.25 and 0.5 percent were considered the weakest strengths, while hydrocortisone 1.0 percent was rated a little higher, equivalent to fluocinolone acetonide 0.01 percent and flurandrenolide 0.025 percent. *The Medical Letter* noted that absolute equivalents of topical steroids have not been established, and some dermatologists might disagree with the positions given to some of the formulations presented in the chart.

The above data show that, in comparison to other steroids, hydrocortisone has been determined to be a low potency drug that is effective for the treatment of many common dermatoses. The Panel concluded that numerous controlled and uncontrolled studies provide strong documentation for the efficacy of hydrocortisone and hydrocortisone acetate for antipruritic and anti-inflammatory use in the 0.5- to 5-percent dosage range. As noted above, the Panel identified a number of effectiveness studies in which the 1-percent concentration of hydrocortisone was used and a high percentage of subject improvement occurred for various dermatoses (44 FR 69768 at 69822).

C. Hydrocortisone 1 Percent Is More Effective Than 0.5 Percent

Seven controlled clinical trails (Refs. 22, 32, 35, 54, 72, 73, and 74) involving over 4,000 subjects with various dermatoses demonstrate that 1 percent hydrocortisone is more effective than the 0.5-percent concentration in many subjects. The methodology used by many of the investigators in these clinical trials was either paired simultaneous comparisons of active vs. placebo or active vs. active, or crossover patterns using actives and/or placebo. The paired simultaneous comparison technique is used to study the effects of different concentrations of active ingredients applied topically on the same subject. In this procedure, subjects having symmetrical skin lesions of closely similar duration, degree, and extent are selected for comparative evaluation of the effects of one product applied on one side of the body vs. another product applied simultaneously on the other side of the body. In certain conditions (e.g., anogenital pruritus), contralateral areas may be in opposition to one another, thus making discrete unilateral topical applications impossible.

The crossover technique is well-known and is an effective way to determine the minimal effective dose of a drug, particularly in conditions that are longstanding and generally unresponsive to previous therapy. In a number of instances where investigators had accepted the therapeutic effectiveness of topical hydrocortisone, crossover comparisons were no longer made to placebo (or previously accepted topical therapy) but were made to higher or lower concentrations of hydrocortisone. This approach provide data on the minimum effective dose for maintenance or cure of the condition.

Frank, Stritzler, and Kaufman (Ref. 72) studied 282 subjects with atopic dermatitis, contact dermatitis, nummular and hand eczema, neurodermatitis, seborrheic eczema, and pruritus ani and vulvae to compare the effects of 0.5- and 1-percent hydrocortisone alcohol. The subjects were treated with two ointments: one containing 0.5-percent hydrocortisone free alcohol and the other containing 1-percent hydrocortisone free alcohol. Whenever possible, contralateral areas were treated with each ointment for comparative evaluation. When contralateral areas could not be treated because of location, both ointments were alternated. Of the 282 subjects using both ointments, 169 found the 0.5-percent and the 1-percent products equally effective, 80 found the 1 percent more effective, and 33 found the 0.5 percent more effective. The authors stated that, in general, the impression was that the 0.5-percent concentration was about 75 percent as effective as the 1-percent concentration. The authors also noted that frequently a better response to the 0.5-percent concentration was obtained in areas where treatment was initiated with the 1-percent product and then maintained with the 0.5-percent product.

Robinson, Robinson, and Strahan (Ref. 22) evaluated the effects of multiple combinations of different vehicles and concentrations of topical hydrocortisone (0.5, 1.0, and 2.5 percent) in the treatment of various dermatoses in 1,655 subjects. Hydrocortisone free alcohol 0.5, 1.0, and 2.5 percent in various vehicles was used on 757 subjects, and hydrocortisone acetate 0.5, 1.0, and 2.5 percent in various vehicles was used on 349 subjects. The results indicated that 0.5 percent hydrocortisone (alcohol and acetate) was effective in 60 percent of the subjects studied. This concentration was also effective in maintaining symptomatic relief when treatment was initiated with a higher concentration. The paired comparison method was used in several cases of extensive atopic dermatitis, with placebo applied to one part of the body and active drug to another part. In subjects with atopic dermatitis, 0.5 percent hydrocortisone proved to be effective for 60 percent, 1 percent was effective for 80 percent, and 2.5 percent effective for 90 percent. The 1- and 2.5-percent concentrations were of great value in the treatment of dermatitis venenata, while the 0.5-percent concentration was not effective. In anogenital pruritis, the improved, partially improved, and not improved results were as follows: 7:2:4 for 0.5 percent, 27:9:6 for 1 percent, and 18:3:2 for 2.5 percent. Robinson, Robinson, and Strahan concluded from this study that both 0.5- and 1-percent hydrocortisone concentrations were useful and that 1 percent was the optimum concentration. The authors also concluded that there is not appreciable difference between the local action of hydrocortisone free alcohol and hydrocortisone acetate.

Rattner (Ref. 35) studied 1,200 subjects having various dermatoses using topical hydrocortisone acetate in various concentrations and bases and comparing them with placebo bases and standard ointments. Whenever possible, simultaneously paired comparisons were made, using the hydrocortisone product on one side of the body and using the base on a similar lesion on the opposite side of the body. One percent hydrocortisone acetate yielded excellent results in a majority of cases of atopic eczema, contact dermatitis, localized neurodermatitis, otitis externa, and pruritus ani. Rattner found the 1-percent concentration (in an ointment base) to be more effective than the 0.5-percent concentration but occasionally less effective than the 2.5-percent concentration. Rattner also reported that no difference in results was observed between the hydrocortisone acetate and the free alcohol preparation.

Irke and Griffin (Ref. 73) used paired simultaneous comparisons in 60 elderly subjects (between 60 and 90 years of age, average 66 years) of combination products containing a fixed amount of neomycin with various concentrations of hydrocortisone from 0.5 to 2.5 percent. The conditions studied included lichen simplex chronicus, anogenital pruritus, severe and prolonged contact dermatitis, seborrheic dermatitis, stasis dermatitis,

infectious eczematoid dermatitis, dishidrosis, and nummular eczema. They found that the 0.5-percent hydrocortisone preparation was the least satisfactory, the 2.5-percent hydrocortisone was the most effective, and the 1-percent hydrocortisone was somewhat less effective than the 2.5-percent but was considered adequate for most conditions studied.

Heilesen, Kristjansen, and Reymann (Ref. 54) in a study of 130 subjects with various dermatoses reported that 0.1- or 0.5-percent concentration of hydrocortisone was not capable of maintaining the effect obtained from using the 1-percent concentration. The authors concluded that the 1-percent concentration seems clearly to mark the threshold of effectiveness.

Welsh and Ede (Ref. 32) compared the effects of 1.0 and 2.5 percent hydrocortisone and its acetate in 402 subjects with chronic dermatoses refractory to other available topical remedies. They found both concentrations adequately treated acute contact dermatitis, mild transient atopic dermatitis, eczema, uncomplicated stasis dermatitis, and pruritus ani. They concluded that the therapeutic effectiveness between the two concentrations was not striking. Later they expanded the study (Ref. 74) and included 306 additional subjects (708 total) with dermatoses known to be refractory to usual treatment. Hydrocortisone ointment (acetate and alcohol) in 0.5-, 1.0-, and 2.5-percent concentrations was used. The alcohol was more effective than the acetate. All three concentrations were effective in treating mild dermatoses, but for very acute or chronic dermatoses only 1 and 2.5 percent were effective. The authors stated that their observations failed to confirm those reported by others, i.e., that the 1-percent concentration clearly marked the threshold of effectiveness, and that 0.5 percent is not capable of maintaining the effects obtained with 1 percent hydrocortisone.

The Panel evaluated 37 studies demonstrating the effectiveness of topical hydrocortisone at concentrations ranging from 0.1 to 2.5 percent. In 22 studies, 1 percent hydrocortisone was the concentration used, and 9 other studies included 1 percent hydrocortisone in a range of concentrations that were evaluated (44 FR 69768 at 69822). The agency notes that five of the seven studies (Refs. 22, 35, 54, 72, and 74) described above were cited by the Panel as supporting the effectiveness of hydrocortisone (44 FR 69822). The agency has determined that these clinical studies demonstrate that a 1-percent concentration of hydrocortisone is more effective than a 0.5-percent concentration for a number of dermatologic conditions that are included in the OTC labeling for products containing this ingredient. However, the agency concludes that a range of concentrations from 0.25 to 1 percent is appropriate for OTC drug products containing hydrocortisone.

IV. Labeling

A. Introduction

Labeling for 0.25 to 0.5 percent hydrocortisone and hydrocortisone acetate was proposed by the agency in the tentative final monograph for OTC external analgesic drug products (48 FR 5852 at 5868 and 5869). It was revised in amendments to that proposed monograph in the **Federal Register** of July 30, 1986 (51 FR 27360 at 27363) and August 5, 1988 (53 FR 32592 at 32593). The labeling contains indications that the agency considers as being amenable for using hydrocortisone for self-treatment, such as "For the temporary relief of itching associted with minor skin irritations * * * and rashes * * *." The proposed warnings and directions applicable to all OTC external analgesic drug products also apply to hydrocortisone, e.g., for external use only and 7-day use limitation. In addition, the following warning is specifically required for OTC hydrocortisone products bearing a label indication for external genital itching or for external feminine itching: "Do not use if you have a vaginal discharge. Consult a" (select one of the following: "physician" or "doctor"). The agency concludes from the safety and effectiveness data presented that the labeling that was proposed for 0.25 to 0.5 percent hydrocortisone, with the modifications described below, would also be appropriate for OTC drug products containing 1 percent hydrocortisone.

B. Proposed OTC Labeling for 1 Percent Hydrocortisone

The citizen petition (Ref. 3) contained proposed labeling for 1 percent hydrocortisone, while the manufacturers' association's (Ref. 4) proposed labeling was for concentrations "up to" 1 percent. The labeling proposed by these two parties is substantially similar to the labeling proposed by the agency for the 0.25- to 0.5-percent concentration of hydrocortisone in the tentative final monograph for OTC external analgesic drug products (48 FR 5852 at 5868) and the amended tentative final monograph (51 FR 27360 at 27363).

The labeling proposed by the petitioner (Ref. 3) for 1 percent hydrocortisone is as follows:

Indications. For the temporary relief of minor skin irritations; inflammation, itches, and rashes due to insect bites; external anal itching; and allergic and irritant dermatitis caused by poison ivy, poison oak, poison sumac, soaps, detergents, cosmetics, or jewelry. Other uses or the use of the product for more than 7 days should be undertaken only under the advice and supervision of a physician.

Warnings. For external use only. Avoid contact with eyes. If the condition being treated worsens, or if symptoms persist for more than 7 days, discontinue use of this product and consult a physician. *Do not use for the treatment of diaper rash* or on children under 2 years of age except under the advice and supervision of a physician. Keep this and all drugs out of the reach of children. In case of accidental ingestion, seek professional assistance or contact a poison center immediately.

Directions for use. For adults and children 2 years of age and older: Apply to affected area not more than 3 or 4 times daily. Do not use in children under 2 years of age except under the advice and supervision of a physician.

The petitioner excluded what it considered "chronic conditions" (i.e., eczema) from the proposed indications for use because it felt that OTC topical hydrocortisone 1 percent should be reserved for short-term use in acute dermatologic conditions, and that conditions requiring therapy for more than 7 days should be treated by a physician. The petitioner also proposed the following new statement: "Other uses or the use of the product for more than 7 days should be undertaken only under the advice and supervision of a physician."

The petitioner stated that the proposed warning "do not use for the treatment of diaper rash * * * except under the advice and supervision of a physician" was based on the Dermatologic Drugs Advisory Committee's concern regarding the potential use of 1 percent hydrocortisone in the treatment of diaper rash. The petitioner considered this to be a valid concern. The petitioner also felt that the warning was necessary to help restrict use of 1 percent hydrocortisone to children 2 years of age and older and adults.

The labeling proposed by the manufacturers' association (Ref. 4) for OTC topical hydrocortisone and hydrocortisone acetate for short-term therapy as antipruritics in concentrations up to 1 percent was as follows:

Indications. For the temporary relief of itching associated with minor skin irritations,

inflammation, and rashes due to (select one or more of the following: eczema, insect bites, poison ivy, poison oak, or poison sumac, soaps, detergents, cosmetics, jewelry, seborrheic dermatitis, psoriasis) and/or (and for external (select one or more of the following: genital, feminine, and anal) itching).

Warnings. For external use only. Avoid contact with the eyes. If condition worsens, or if symptoms persist for more than 7 days or clear up and occur again within a few days, do not use this or any other hydrocortisone product unless you have consulted with a (physician/doctor). Do not use on children under 2 years of age except under the advice and supervision of a physician. Do not use if you have a vaginal discharge. Consult a (physician/doctor). (Only if indications include genital or feminine itching.)

Directions. Adults and children 2 years of age and older: Apply to affected area not more than 3 to 4 times daily. For children under 2 years of age there is no recommended dosage except under the advice and supervision of a physician.

There are some differences in these two proposed labels for OTC hydrocortisone drug products. The indications for itching due to "eczema," "seborrheic dermatitis," "psoriasis," "genital," and "feminine" itching were included in one proposal, but excluded in the other proposal. The phrase "* * * do not use this or any other hydrocortisone product unless you have consulted with a (physician/doctor)" was proposed as an addition to the 7 day limit-of-use warning by the manufacturers' associations for the reason that this additional wording is more directly informative and instructional to the consumer, particularly with market availability of OTC hydrocortisone at several concentrations. The other proposal contained a similar statement: "Other uses or the use of the product for more than 7 days should be undertaken only under the advice and supervision of a physician."

The agency believes that the labeling proposed for hydrocortisone and hydrocortisone acetate should apply to and be the same for all concentrations (0.25 to 1.0 percent), just as the labeling proposed for hydrocortisone and hydrocortisone acetate in the tentative final monograph for OTC external analgesic drug products applies to both 0.25 and 0.5 percent concentrations (48 FR 5852 at 5868 and 5869, 51 FR 27360 at 27363, and 53 FR 35292 at 35293).

The agency has considered the two labeling proposals and determined that they are not significantly different in concept from the labeling that the agency has proposed for hydrocortisone in § 348.50 in the tentative final monograph for OTC external analgesic drug products. The agency's original proposal in 1983 (48 FR 5868) did not include seborrheic dermatitis or psoriasis as indications. In the **Federal Register** of July 30, 1986 (51 FR 27360), the agency amended the indications in § 348.50(b)(3) (i) and (ii) of the tentative final monograph to include seborrheic dermatitis and psoriasis as conditions for which hydrocortisone at 0.25- to 0.5-percent concentration can be labeled for OTC use. The agency has determined that "eczema" can remain the OTC labeling for these products because many of the safety and effectiveness studies described above involved the treatment of eczematous conditions, with improvement evident within a week. (See Part II. above—Safety and Part III. above—Effectiveness.) In addition, the 7-day limit of use warning is intended to prevent long-term use of hydrocortisone for any indication, such as "eczema," without consulting a physician/doctor. Therefore, the agency is proposing that the indications in § 348.50(b)(3) (i) and (ii), as amended in 1986, be used for all concentrations of hydrocortisone from 0.25 to 1 percent. These indications are currently proposed as follows: (i): "For the temporary relief of itching associated with minor skin irritations and rashes" [which may be followed by: "due to" (select one or more of the following: "eczema," "insect bites," "poison ivy, poison oak, or poison sumac," "soaps," "detergents," "cosmetics," "jewelry," "seborrheic dermatitis," "psoriasis") and/or ("and for external" (select one or more of the following, "genital," "feminine," and "anal") "itching")].

(ii): "For the temporary relief of itching associated with minor skin irritations, inflammation, and rashes due to" (select one or more of the following: "eczema," "insect bites," "poison ivy, poison oak, or poison sumac," "soaps," "detergents," "cosmetics," "jewelry," "seborrheic dermatitis," "psoariasis)," and/or ("and for external" (select one or more of the following: "genital," "feminine," and "anal") "itching").

The agency believes that part of the statement "other uses or the use of this product (for more than 7 days) should be undertaken only under the advice and supervision of a physician," proposed by the petitioner for inclusion with the indications, may help prevent misuse of hydrocortisone for cuts, blisters, infections, etc. (nonindications), which could result in adverse reactions. Accordingly, the agency is amending proposed § 348.50(b)(3) to add paragraph (iii) to read: "Other uses of this product should be only under the advice and supervision of a" (select one of the following: "physician" or "doctor"). The agency is not including the words "for more than 7 days" because it believes that these words might inadvertently encourage use of the product for more than 7 days.

The agency agrees with the manufacturers' association that addition of the phrase "* * * do not use this or any other hydrocortisone product unless you have consulted a (physician/doctor)" to the 7 day limit-of-use warning will be helpful to consumers because of the proposed availability of hydrocortisone for OTC use at concentrations ranging from 0.25 to 1 percent. Accordingly, the agency is revising proposed § 348.50(c)(7) to add paragraph (i), to read as follows:

(7) *For products containing hydrocortisone preparations identified in § 348.10(d) (1) and (2).* (i) "If condition worsens, or if symptoms persist for more than 7 days or clear up and occur again within a few days, do not use this or any other hydrocortisone product unless you have consulted a" (select one of the following: "Physician" or "doctor").

The warning currently proposed in § 348.50(c)(7) in the tentative final monograph (February 8, 1983; 48 FR 5852 at 5869) for products with an indication for external "genital or feminine itching" will be redesignated as § 348.50(c)(7)(ii).

Other warnings being included in this proposed amendment apply to products for "external anal itching." In the **Federal Register** published August 25, 1988 (53 FR 32592 at 32593), the agency amended the tentative final monograph for OTC external analgesic drug products to include the hydrocortisone-containing products warnings and directions proposed in § 348.50(c) (2), (3), and (4), and (d)(1) of the tentative final monograph for OTC anorectal drug products. These warnings are now being included in § 348.50(c)(7)(iii), instead of (c)(9) as previously designated, and read: "For products containing hydrocortisone preparations identified in § 348.10(d) (1) and (2) that are labeled with the indication' * * * for external anal itching." In addition to the warnings in paragraph (c)(1) of this section, the labeling of the product also contains the warnings proposed in § 348.50(c) (2), (3), and (4) of this chapter. (See the **Federal Register** of August 15, 1988; 53 FR 30756.)"

The agency notes that the Panel did not discuss the use of hydrocortisone for the treatment of diaper rash. The Miscellaneous External Panel briefly mentioned the use of 0.5 to 1 percent hydrocortisone for the treatment of severe diaper rash by physicians (47 FR 39412 at 39416).

The agency believes that the proposed warning "do not use for the treatment of diaper rash or on children under 2 years of age except under the advice and supervision of a physician" is appropriate, even though diaper rash is not an indication in the tentative final monograph for OTC external analgesic drug products, and the directions state not to use on children under 2 years of age. The Panel advised that products containing any external analgesic active ingredient not be used on children under 2 years of age except under the advice and supervision of a physician. The Panel's main concern was related to increased cutaneous penetration of a drug under the occlusive conditions found in infants resulting from a diaper, lying on a waterproof mattress, wet clothing, or from body folds touching each other. The Panel noted that the penetration of hydrocortisone is enhanced 10- to 100-fold by occlusion, and that ingredients under occlusion may possibly be corrosive to the infant's skin (44 FR 69768 at 69773 and 69774).

The agency is aware that children over 2 years of age may also have diaper rash (Refs. 75, 76, and 77). The above warning would also alert parents of children over 2 years of age not to use hydrocortisone-containing drug products for diaper rash unless directed to do so by a physician. The agency believes possible enhanced penetration of hydrocortisone could also be a potential problem if an occlusive environment existed in a child over 2 years of age. Accordingly, the agency is proposing a new paragraph (iv) in § 348.50(c)(7) to read: "Do not use for the treatment of diaper rash. Consult a" (select one of the following: "physician" or "doctor"). The agency invites comments regarding this proposed warning.

External analgesic drug products for diaper rash use were evaluated by the Miscellaneous External Panel in an advance notice of proposed rulemaking published in the **Federal Register** of September 7, 1982 (47 FR 39412). The agency will present its tentative findings on these products, which includes hydrocortisone-containing products, in a future issue of the **Federal Register.**

Based on the Panel's concerns about drug penetration being enhanced under occlusion, the agency believes that it may be appropriate to revise and clarify the directions for use applicable to all OTC external analgesic drug products in § 348.50(d)(1) for children under 2 years of age. The agency believes it would be appropriate to add the words "do not use" in addition to the instruction to "consult a physician (or doctor)." Accordingly, the agency is revising the general directions that apply to all OTC external analgesic drug products (which includes hydrocortisone) in proposed § 348.50(d)(1) to read as follows: * * * "Adults and children 2 years of age and older: Apply to affected area not more than 3 to 4 times daily. Children under 2 years of age: Do not use, consult a" (select one of the following: "physician" or "doctor").

The agency tentatively concludes that the changes proposed in this amendment should result in labeling that is clear to consumers and that assures safe and proper self-use of OTC topical hydrocortisone drug products up to 1-percent concentration. Because OTC marketing of hydrocortisone is a prescription-to-OTC switch, agency regulations in 21 CFR 330.13(b)(2) require that such a product be marketed with labeling that is in accord with a proposed monograph or a tentative final monograph. Accordingly, the labeling proposed in 1979 (44 FR 69768 at 69865 and 69866) or 1983 (48 FR 5852 at 5868 and 5869), as amended in 1986 (51 FR 27360 at 27363) and in 1988 (53 FR 32592 at 32593), should continue to be used for OTC hydrocortisone-containing drug products. This document, while it does not allow OTC marketing of products containing above 0.5 percent hydrocortisone up to 1 percent hydrocortisone, does apply to currently marketed products containing 0.25 to 0.5 percent hydrocortisone. Irrespective of the final decision on OTC status of hydrocortisone above 0.5 percent up to 1 percent, the agency intends for the labeling revisions proposed in this document to apply to OTC drug products containing 0.25 to 0.5 percent hydrocortisone. Accordingly, manufacturers may use the labeling proposed in this amendment on currently marketed OTC hydrocortisone-containing drug products. The final monograph, when published, will establish the final labeling that will be required for all OTC drug products that contain hydrocortisone.

C. Differentiation Between Product Strengths in OTC Labeling

Based on the market availability of multiple strengths of other OTC external and internal drug ingredients, the manufacturers' association indicated that packaging graphics will clearly communicate to consumers that there is a difference in strength of OTC drug products containing hydrocortisone. The use of terms such as "Regular Strength" and "Maximum Strength" was suggested so that consumers would be able to treat indicated itch/rash conditions with what they determined to be the appropriate product concentration for their specific needs.

The agency recognizes that currently there are OTC drugs on the market containing varying concentrations of active ingredients per dosage unit. Although terms such as "regular strength" and "maximum strength" may be helpful to consumers by alerting them to the fact that products with such labeling may not necessarily contain the quantity of ingredient contained in other products they have purchased, the agency believes such terms and other similar terms are only peripherally related to an OTC drug product's safety and effectiveness. Therefore, the agency considers such terms to be outside the scope of the OTC drug review and is not including such terms in the monograph.

The agency is aware that the term "maximum strength" currently appears in the labeling of some 0.5 percent OTC hydrocortisone drug products. The agency is concerned about the degree of confusion that may be caused to consumers if products containing 0.5 percent hydrocortisone are relabeled to state "regular strength" without further explanation regarding the change. It is possible that the same entity (a 0.5-percent hydrocortisone product), marketed by either the same manufacturer or different manufacturers, could appear on the store shelf side-by-side with different labeling: one stating that the product is "regular strength" and the other stating that the same strength product is "maximum strength." Further, referring to 1 percent hydrocortisone as "maximum strength" could not only be confusing but also be considered misleading because there are higher concentrations of hydrocortisone available by prescription. In addition, the agency questions which term would be used to designate the 0.25-percent concentration of hydrocortisone and any concentrations in between 0.25 percent and 1 percent, which might be marketed under the OTC drug monograph. Based on the above, if these terms are used in the labeling of OTC hydrocortisone-containing drug products, the agency believes that an adequate explanation of their meaning should be provided to consumers.

As stated above, these terms will not be included in the labeling required by the monograph for OTC external analgesic drug products, but they could be used elsewhere in the labeling. However, if such terms are used, the agency believes manufacturers should provide consumers with an explanation of these terms as they relate to these specific products. In accordance with

§ 201.62(a) (21 CFR 201.62(a)), the concentration of the hydrocortisone present should be included in the labeling to give accurate information about the strength of the drug in a specific package.

V. Suitable Dosage Forms

A. Introduction

The Panel emphasized that vehicles play an important role in the safety and effectiveness of dermatological drug products (44 FR 69768 at 69774 and 69775). Vehicles were discussed as one of the physiochemical factors that affect skin penetration. The Panel believed that the vehicle in which an active ingredient or combination of ingredients is incorporated may influence effectiveness. The Panel stated that the vehicle must provide solubility, stability, maintain contact of the active ingredient with the lesion of the skin, and must not retard passage of the drug into the skin or lesions, thereby decreasing bioavailability. A drug's rate of release from its vehicle depends on its rate of diffusion within the vehicle. A vehicle may also affect the hydration of the stratum corneum. Those which increase or maintain hydration usually promote drug absorption. Dimethylsulfoxide (DMSO) and dimethylformamide (DMF), used as vehicles, may accelerate absorption of substances through the skin barrier. Surface active ingredients (surfactants) also increase absorption. Most vehicles consist of emulsions, i.e., suspensions of droplets of one liquid in another in which it is insoluble. Ointments, pastes, or creams are semisolid vehicles. Oleaginous vehicles consist of hydrocarbons, fatty acids, or esters of fatty acids. The Panel determined that ideal dermatological vehicles are stable, neutral, nongreasy, nondegreasing, nonirritating, nondehydrating, nondrying, washable, odorless, and stainless. Additionally, vehicles should act efficiently on all kinds of human skin, hold at least 50 percent water, and should be easily compounded with known chemicals. The Panel recommended that all inactive ingredients, including those in vehicles, be listed in the drug products' labeling.

B. The Panel's Discussion of Vehicles in Relation to Hydrocortisone

In its discussion of hydrocortisone, the Panel referred to vehicles a number of times. The Panel cited the **Federal Register** of April 28, 1971 (36 FR 7982) as containing a statement that 0.5-, 1.0-, and 2.0-percent hydrocortisone products in different types of vehicles were generally recognized as safe and effective (44 FR 69768 at 69813). The Panel mentioned a study in which hydrocortisone solutions or suspensions in several vehicles (i.e., polyethylene glycol, olive oil, chloroform plus olive oil, physiological saline, or ointment base) were applied to shaved backs of female rats (44 FR 69816). No significant difference in results among the various vehicles was detected. Adverse reactions in some studies were attributed to the vehicle or a contaminant (44 FR 69817). Also, vehicles have been implicated in sensitivity and irritation reactions with hydrocortisone (44 FR 69822). At its 23d meeting held on March 4 and 5, 1976 (Ref. 7), the Panel decided that its report on hydrocortisone was to include a recommendation: "Not to be incorporated in vehicles greatly enhancing cutaneous penetration such as DMSO and related compounds." This statement was considered necessary in view of the possibility of future development of new vehicles and formulations which may enhance absorption and the effectiveness of topically applied medicaments.

At its 24th meeting held on May 19 and 20, 1976 (Ref. 78), the Panel again expressed concern regarding the use of new vehicles, with properties similar to DMSO, which may increase absorption of ingredients beyond what the Panel determined to be safe and effective. The Panel concluded at that meeting that "Ingredients reviewed by this Panel were categorized on the basis of their use in currently employed topical vehicles," (Ref. 78).

C. Discussion of Vehicles in Submissions

OTC drug monographs do not, as a general rule, identify a formulation (vehicles) for dosage forms containing monograph active ingredients. Although vehicles are considered to be inactive ingredients, the Panel noted that many vehicles interact physically and chemically with the outer layer of human skin. The substantivity, penetration, and resistance of the active ingredients to sweating, washing, and other factors often depend upon the vehicle (44 FR 69768 at 69775). The OTC drug regulations in 21 CFR 330.1(e) address vehicles in OTC drug products by stating that a product may contain only suitable inactive ingredients which are safe and do not interfere with the effectiveness of the preparation or with suitable tests or assays to determine if the product meets its professed standards of identity, strength, quality, and purity.

The petitioner (Ref. 3) did not address vehicles used in OTC hydrocortisone containing drug products, but the manufacturers' association (Ref. 4) referred to the comprehensive examination and discussion of vehicles in the Panel's report on OTC external analgesic drug products, published in the **Federal Register** of December 4, 1979 (44 FR 69768), and the published clinical studies evaluated by the Panel as supporting the lack of effects of vehicles on percutaneous absorption of hydrocortisone. The manufacturers' association contended that the studies show that under normal conditions of use, topically applied hydrocortisone is only minimally absorbed systemically. (See also part II. paragraph C. above—*Systemic Effects and Risk of Superinfection.*) Two studies (Refs. 79 and 80) were cited as showing that only 1 percent or less of the amount of hydrocortisone applied is absorbed through normal adult skin and that 2 percent is absorbed through damaged skin. In one study (Ref. 79), the amount and rate of penetration of ^{14}C hydrocortisone applied to normal skin was evaluated by measuring excretion in the urine over a period of 10 days. The authors commented that urinary excretion of ^{14}C hydrocortisone accurately reflects the penetration of ^{14}C hydrocortisone through the epidermis because excretion of ^{14}C after intraveous or intradermal injection is very rapid with little delay when compared to any method of topical application. This is further confirmed by the relatively efficient recovery of 63 to 75 percent of the drug. The authors concluded that their data confirm that less than 1 percent of topically applied hydrocortisone is absorbed through intact skin and that this absorption is spread out as long as 10 days.

The other study (Ref. 80) was a preliminary and short, but similar, report involving only 2 subjects. Peak excretion of hydrocortisone 4-C^{14} in an ointment base occurred in the second 24 hours after application, but lower levels of radioactivity persisted throughout the 6-day experimental period. The authors concluded that while precise quantitative data could not be determined under the conditions of the experiment, less than 1 percent of the topically applied 4-C^{14} hydrocortisone was excreted in the urine over a period of 6 days. It was postulated, based on this excretion pattern, that a depot of hydrocortisone forms, possibly in the skin, which persistently releases small amounts of the hormone over an extended period of time.

The manufacturers' association calculated a "worst case scenario" where topical application of one ounce

of product (entire OTC package quantity) at one time would lead to absorption of only 300 mg of hydrocortisone if all the drug were absorbed, which would not occur. The association stated that this quantity of hydrocortisone is only slightly higher than the initial dosage of 20 to 240 mg a day approved by FDA in the labeling of orally-administered hydrocortisone tablets. Based on the amount of data on vehicles for hydrocortisone products reviewed by the Panel, the manufacturers' association reasoned that neither the Panel nor the agency saw a need to limit or specify the types of dermatologic vehicles appropriate for OTC 0.5 percent hydrocortisone. The manufacturers' association concluded that any of the commonly available dermatological vehicles would be appropriate for the safe and effective delivery of 1 percent hydrocortisone in an OTC drug product.

The agency agrees with the Panel's recommendation that hydrocortisone for OTC use should be incorporated into vehicles that do not greatly enhance percutaneous absorption with the resulting possibility of causing safety risks. The agency also agrees with the Panel, in its discussion of vehicles, that all inactive ingredients in the product (including those in vehicles) be listed on the labeling of OTC drug products (44 FR 69768 at 69775). Such information would help consumers avoid products containing ingredients to which they are allergic or sensitive. Hydrocortisone safety studies discussed above indicated that most sensitization and irritancy reactions were caused by the vehicle. (See also part II. paragraph D. above—*Sensitization and Irritation Potential of Hydrocortisone.*) The agency also notes that some vehicles decrease penetration, diminishing availability of the drug to the skin. As stated above, the OTC drug regulations in 21 CFR 330.1(e) should be used as the basis for formulating OTC hydrocortisone drug products.

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(3) Comment No. CP00005, Docket No. 78N–0301, Dockets Management Branch.

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VI. Summary of the Agency's Changes

FDA has considered the comments in the citizen petition (Ref. 3) and from the manufacturers' association (Ref. 4), and other relevant information. The agency is amending the tentative final monograph to include conditions for OTC use of hydrocortisone and its hydrocortisone acetate equivalent in concentrations above 0.5 up to 1 percent based on its evaluations of the data and other changes described in the summary below. A summary of the changes made by the agency follows.

1. The agency is revising § 348.10(d)(1) to read as follows: "Hydrocortisone, 0.25 to 1 percent."

2. The agency is revising § 348.10(d)(2) to read as follows: "Hydrocortisone acetate, equivalent to hydrocortisone, 0.25 to 1 percent."

3. In the tentative final monograph published on February 8, 1983, the spray dosage form was not included in the statement of identity proposed in § 348.50(a)(2). The agency listed several examples of appropriate dosage forms, e.g., cream, lotion, or ointment. The agency is expanding this list to also include a spray dosage form.

Accordingly, the agency is amending § 348.50(a)(2) to read "The labeling identifies the product as "antipruritic (anti-itch)," "anti-itch," "antipruritic (anti-itch) (insert dosage form, e.g., cream, lotion, ointment, or spray)," or "anti-itch (insert dosage form, e.g., cream, lotion, ointment, or spray)."

4. The agency is proposing that the indications in § 348.50(b)(3) (i) and (ii), as amended on July 30, 1986 to include seborrheic dermatitis and psoriasis (51 FR 27360 at 27363), be used for all OTC concentrations of hydrocortisone and hydrocortisone acetate.

5. To help prevent misuse of OTC hydrocortisone drug products, with possible resultant adverse reactions, the agency is proposing an additional statement in § 348.50(b)(3), as paragraph (iii), to read as follows: "Other uses of this product should be only under the advice and supervision of a" (select one of the following: "physician" or "doctor").

6. The agency is proposing that the 7-day limit of use warning in § 348.50(c)(1)(iii) not be used for OTC hydrocortisone drug products. In its place, hydrocortisone drug products will bear a somewhat different warning, which is being incorporated in § 348.50(c)(7)(i), to read as follows: "If condition worsens, or if symptoms persist for more than 7 days or clear up and occur again within a few days, do not use this or any other hydrocortisone product unless you have consulted a" (select one of the following: "physician" or "doctor").

7. The agency is proposing to redesignate the current warning for hydrocortisone products in § 348.50(c)(7) as paragraph (7)(ii).

8. The agency is proposing to redesignate the current warnings for hydrocortisone products in § 348.50(c)(9) as (c)(7)(iii).

9. The agency is proposing to add the warning "Do not use for the treatment of diaper rash. Consult a" (select one of the following: "physician" or "doctor") to § 348.50(c)(7) as paragraph (iv). Because children over 2 years of age may get diaper rash, the agency believes this warning will alert parents not to use OTC hydrocortisone products for diaper rash for children of any age, without first consulting a doctor.

10. The agency proposes to add the instruction "do not use" to the general directions for all OTC external analgesic drug products (including hydrocortisone) because it better alerts consumers about use of these products on children under 2 years of age and makes an additional warning unnecessary. The proposed revision in § 348.50(d)(1) reads: * * * "Directions": (1) Adults and children 2 years of age and older: Apply to affected area not more than 3 to 4 times daily. Children under 2 years of age: Do not use, consult a" (select one of the following: "physician" or "doctor".)

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed amendment of the OTC external analgesic drug products tentative final monography, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act (Pub. L. 96–354). That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC external analgesic drug products is not expected to pose such as impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC hydrocortisone external analgesic drug products. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC hydrocortisone external analgesic drug products should be accompanied by appropriate documentation. A period of 60 days from the date of publication of this proposed rulemaking in the **Federal Register** will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday. This action was considered under FDA's final rule implementing the National Environmental Policy Act (21 CFR part 25).

Interested persons may, on or before April 30, 1990, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Room 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before April 30, 1990. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register**.

In establishing a final monography, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on April 30, 1990. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR Part 348

External analgesic drug products, Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act it is proposed that subchapter D of chapter I of title 21 of the Code of Federal Regulations be amended in part 348 (as proposed in the **Federal Register** of February 8, 1983; 48 FR 5852) as follows:

PART 348—EXTERNAL ANALGESIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR part 348 is revised to read as follows:

Authority: Secs. 201, 501 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

2. Section 348.10 is amended by revising paragraphs (d) (1) and (2) to read as follows:

§ 348.10 Analgesic, anesthetic, and antipruritic active ingredients.

* * * * *

(d) * * *

(1) Hydrocortisone, 0.25 to 1 percent.

(2) Hydrocortisone acetate, equivalent to hydrocortisone, 0.25 to 1 percent.

* * * * *

3. Section 348.50 is amended by revising paragraph (a)(2), by adding new paragraph (b)(3)(iii), by revising the heading for paragraph (c)(1), by revising paragraph (c)(7), and by revising paragraph (d)(1) to read as follows:

§ 348.50 Labeling of external analgesic drug products.

(a) * * *

(2) *For products containing hydrocortisone or hydrocortisone acetate identified in § 348.10(d).* The labeling identifies the product as "antipruritic (anti-itch)," "anti-itch," "antipruritic (anti-itch) (insert dosage form, e.g., cream, lotion, ointment, or spray)," or "anti-itch (insert dosage form, e.g., cream, lotion, ointment, or spray)."

* * * * *

(b) * * *

(3) * * *

(iii) "Other uses of this product should be only under the advice and supervision of a" (select one of the following: "physician" or "doctor").

* * * * *

(c) * * *

(1) *For products containing any external analgesic active ingredient identified in § 348.10 (a), (b), and (c) and § 348.12.* * * *

* * * * *

(7) *For products containing hydrocortisone preparations identified in § 348.10(d) (1) and (2).* (i) "If condition worsens, or if symptoms persist for more than 7 days or clear up and occur again within a few days, do not use this or any other hydrocortisone product unless you have consulted a" (select one of the following: "physician" or "doctor").

(ii) *For products that are labeled with this indications "* * * for external genital itching," or "* * * for external feminine itching."* "Do not use if you have a vaginal discharge. Consult a" (select one of the following: "physician" or "doctor").

(iii) *For products containing hydrocortisone preparations identified in § 348.10(d) (1) and (2) that are labeled with indication "* * * for external anal itching."* In addition to the warnings in paragraph (c)(1) of this section, the labeling of the product also contains the warnings proposed in § 346.50(c) (2), (3), and (4) of this chapter. (See the **Federal Register** of August 15, 1988; 53 FR 30756.)

(iv) "Do not use for the treatment of diaper rash. Consult a" (select one of the following: "Physician" or "doctor").

* * * * *

(d) * * *

(1) Adults and children 2 years of age and older: Apply to affected area not more than 3 to 4 times daily. Children under 2 years of age: Do not use, consult a (select one of the following: physician or doctor).

* * * * *

Dated: February 14, 1990.

James S. Benson,

Acting Commissioner of Food and Drugs.

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